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**WO 02/102313 A2**

(54) Title: PYRIMIDINE INHIBITORS OF PHOSPHODIESTERASE (PDE) 7

(57) Abstract: Pyrimidine phosphodiesterase 7 (PDE 7) inhibitors of the following formula [insert chemical structure here] wherein R₁, R₂, Z, J and L are described herein, and analogs thereof are provided which are useful in treating T-cell mediated diseases.

Pyrimidine Inhibitors of Phosphodiesterase (PDE) 7

Field of the Invention

The present invention relates to pyrimidine inhibitors of phosphodiesterase 7 (PDE 7) (including both selective inhibitors of PDE 7, and dual inhibitors of PDE 7 and phosphodiesterase 4), pharmaceutical compositions containing these inhibitors, and the use of these inhibitors in the treatment of leukocyte activation-associated or leukocyte-activation mediated disease and inflammatory diseases either alone or in combination with other therapeutic agents.

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Background of the Invention

Phosphodiesterases (PDEs) hydrolyze the second messenger molecules cAMP and cGMP to affect cellular signaling. At least 11 families of PDEs exist, some of which (PDE3,4,7,8) are specific for cAMP, and others (PDE5,6,9) for cGMP. Further family members (PDE1,2,10,11) have dual specificity. A recent publication demonstrated a role for PDE7 in the activation and/or proliferation of T cells (*Li, Yee and Beavo, Science 283:848-851, 1999*). Resting T lymphocytes express mainly PDE3 and PDE4. However, upon activation, T cells dramatically upregulate PDE7 and appear to rely on this isozyme for regulation of cAMP levels. Removal of the ability to upregulate the production of PDE7 protein by anti-sense oligonucleotides inhibited the proliferation and IL-2 production along with the maintenance of high concentrations of intracellular cAMP in CD3xCD28 stimulated T cells.

A PDE7 inhibitor is defined herein as a compound for which the IC₅₀ of the compound in a PDE7 inhibition assay is less than 20 micromolar (preferably less than 25 10 micromolar, more preferably less than 5 micromolar, most preferably less than 1 micromolar). The PDE7 IC₅₀ of a selective PDE7 inhibitor should be less than one-tenth the IC₅₀ of said compound in all of the following PDE assays: PDE1, PDE3 and PDE4 (more preferably the PDE7 IC₅₀ of a selective PDE7 inhibitor should be less than one-twentieth the IC₅₀ of said compound in the following PDE assays: PDE1 and PDE3, most 30 preferably the PDE7 IC₅₀ of a selective PDE7 inhibitor should be less than one-hundredth the IC₅₀ of said compound in a PDE3 assay).

Several isoforms of PDE1 have been identified and are distributed in heart, lung, and kidney tissue, as well as in circulating blood cells and smooth muscle cells. PDE1 inhibitors have demonstrated potent vasodilator activity. Such activity would represent an undesirable side effect in a therapeutic agent with the utilities listed in this patent for a PDE7 inhibitor. The PDE3 family of enzymes are distributed in several tissues including the heart liver, and platelets. PDE3 inhibitors have demonstrated potent cardiac iotropic activity. Such activity would represent an undesirable side effect in a therapeutic agent with the utilities listed in this patent for a PDE7 inhibitor. Several isoforms of PDE4 exist, and these are expressed in a wide variety of tissues including heart, kidney, brain, the gastrointestinal track and circulating blood cells. PDE4 inhibitors have demonstrated clinical utility for COPD, and have also been suggested to have utility for rheumatoid arthritis, and multiple sclerosis, and to possess anti-inflammatory activity. The utility of PDE4 inhibitors has been limited to some extent by their propensity to cause emesis. As such there are circumstances where it would be desirable to develop PDE7 inhibitors, which have a degree of selectivity against PDE. A selective inhibitor of PDE7 is expected to have broad application as an immunosuppressant in T cell-mediated diseases. PDE7 inhibitors will act at a different stage of the T cell signaling process compared to current immunosuppressants by inhibiting a very early stage of the T cell activation cascade. A selective inhibitor of PDE7 is also expected to have a decreased potential for clinically significant side effects compared to current immunosuppressants, therefore the primary disease indications are solid organ transplantation (SOT) and rheumatoid arthritis. Additional indications may include IBD, psoriasis, asthma and lupus.

A dual PDE7-PDE4 inhibitor (PDE4/7 or PDE7/4) is defined herein as any compound which has an IC₅₀ in both a PDE7 and a PDE4 inhibition assay of less than 20 micromolar (preferably less than 10 micromolar, and more preferably less than 5 micromolar and most preferably less than 1 micromolar), and an IC₅₀ in a PDE3 inhibition assay which is at least 10 times higher than the IC₅₀ of the compound in the PDE7 assay (more preferably at least 20 times higher than the IC₅₀ of the compound in the PDE7 assay, and most preferably at least 100 times higher than the IC₅₀ of the compound in the PDE7 assay). A dual PDE4/7 inhibitor should have a ratio of inhibition

or PDE7 IC₅₀ divided by PDE4 IC₅₀ of between one-tenth and 100. Inhibitors that exhibit such a ratio of inhibition include those that inhibit PDE3, PDE4 and PDE7 as described above, and further inhibit PDE1 at an IC₅₀ at least 10 times higher than the IC₅₀ of the compound in a PDE7 assay (more preferably at least 20 times higher than the
5 IC₅₀ of the compound in the PDE7 assay, and most preferably at least 100 times higher than the IC₅₀ of the compound in the PDE7 assay). Preferred dual PDE7-PDE4 inhibitors further include those compounds that inhibit PDE3, PDE4 and PDE7 as described above, and further suppress both T cell proliferation, and TNF-alpha secretion from either THP-1 monocytes or human peripheral blood mononuclear cells at a level of
10 less than 20 micromolar.

15 "Leukocyte activation" is defined herein as any or all of leukocyte (T cell, monocyte macrophage, neutrophil etc.) cell proliferation, cytokine production, adhesion protein expression, and production of inflammatory mediators. This is mediated in part by the action of PDE4 and/or PDE7 depending on the particular leukocyte under consideration.

20 Examples of leukocyte activation associated or leukocyte activation mediated disorders include transplant rejection, graph verses host disease, and autoimmune disorders, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, COPD, asthma, and inflammatory bowel disease, T-cell mediated hypersensitivity diseases, ischemic or reperfusion injury, and T-cell proliferative disorders.

25 Dual PDE4/7 inhibitors would be expected to block the T cell component of a disease as well as possess anti-inflammatory activity. Thus a dual PDE4/7 inhibitor which is not significantly limited by emesis, may be more effective than either a selective PDE4 inhibitor or a selective PDE7 inhibitor in a variety of disease states such as rheumatoid arthritis, asthma, COPD and multiple sclerosis.

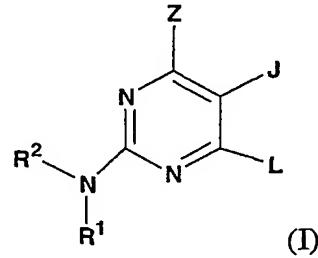
Development of either selective PDE7 inhibitors, or dual PDE7-PDE4 inhibitors will yield novel classes of therapeutics and have a novel mechanism of action by maintaining high levels of intracellular cAMP. These inhibitors would target a major unmet medical need in an area where current therapies possess significant toxicity.

30 Two PDE7 genes have been identified. PDE7A (EC 3.1.4.17) has two isoforms generated by alternate splicing; PDE7A1 restricted mainly to T cells and the

brain, and PDE7A2 for which mRNA is expressed in a number of cell types including muscle cells. The isoforms have different sequence at the amino termini, and it is thought that this portion of each molecule is likely to be important for cellular localization of the enzyme. However, the catalytic domain of each PDE7A enzyme is identical (*Han, P., Zhu, X. and Michaeli, T. Alternative splicing of the high affinity cAMP-specific phosphodiesterase (PDE7A) mRNA in human skeletal muscle and heart. J. Biol. Chem.* 272 (26), 16152-16157 (1997)). Although abundant PDE7A2 mRNA has been identified, the presence of active enzyme in tissues is controversial, as no convincing data shows PDE7A2 protein *in situ* in the adult. PDE7B (EC 3.1.4.17), a second PDE7 gene family member, has approximately 70% homology to PDE7A in the enzymatic core (*Sasaki, T., Kotera, J., Yuasa, K. and Omori, K. Identification of human PDE7B, a cAMP-specific phosphodiesterase Biochem. Biophys. Res. Commun.* 271 (3), 575-583 (2000)). Two patents from Cold Spring Harbor Labs (US 5527896 and US 5977305) cover the methods of preparation and use of recombinant PDE7A protein. A recent publication describes moderately active PDE7 inhibitors (J. Med Chem. Vol. 43, 683 (2000)). WO 00/68230 discloses certain 1,9 dihydropurin-6-ones derivatives as PDE7 inhibitors.

Summary of the Invention

The present invention provides pyrimidine compounds of the following formula (I), their enantiomers, diastereomers, tautomers and pharmaceutically acceptable salts, prodrugs and solvates thereof, for use as PDE7 inhibitors and dual PDE4/7 inhibitors:



wherein

- 25 R¹ is H or alkyl;
- R² is

- (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T¹, T², T³;
- (b) aryl substituted with one to three groups T¹, T², T³ provided that at least one of T¹, T², T³ is other than H; or
- 5 (c) aryl fused to a heteroaryl or heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T¹, T², T³;

Z is

- (a) -OR⁴, -C(O)R⁴, -C(O)OR⁴, -SR⁴, -NR³R⁴, -C(O)NR³R⁴, -NR³SO₂R^{4c} halogen, nitro, haloalkyl; or
- 10 (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T^{1a}, T^{2a}, T^{3a},

J is

- (a) hydrogen, halo, -OR^{4a}, or
- (b) alkyl, alkenyl, or alkynyl any of which may be optionally substituted with one 15 to three groups T^{1b}, T^{2b} or T^{3b};

L is

- (a) hydrogen, -OR^{4b}, -C(O)R^{4b}, -C(O)OR^{4b}, -SR^{4b}, -NR⁵R⁶, -C(O)NR⁵R⁶, -NR⁵SO₂R^{4d}, halogen, haloalkyl, nitro, or
- (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be 20 optionally substituted with one to three groups T^{1c}, T^{2c} or T^{3c};

R³ and R⁴ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T^{1a}, T^{2a} or T^{3a};

25 or R³ and R⁴ together with the nitrogen atom to which they are attached may combine to form a 4 to 8 membered heterocyclo ring optionally substituted with one to three groups T^{1a}, T^{2a} or T^{3a};

R^{4a} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocyclo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be 30 optionally substituted with one to three groups T^{1b}, T^{2b} or T^{3b};

R^4 is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocyclo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be substituted.

D^{4c} , D^{4d} , and D^{4e} are each optionally substituted with one to three groups R'_1 , R'_2 or R'_3 .

5 (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl
any of which may be optionally substituted with one to three groups T^{1a} , T^{2a} or
 T^{3a} .

R^5 and R^6 are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl,

(heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl

any of which may be optionally independently substituted where valence allows with one to three groups T^{1c} , T^{2c} or T^{3c} ;

or R⁵ and R⁶ together with the nitrogen atom to which they are attached may combine to form a 4 to 8-membered heterocyclo ring optionally substituted with one to three groups T^{1c}, T^{2c} or T^{3c};

15 T^{1-1c} , T^{2-2c} , and T^{3-3c} are each independently

(1) hydrogen or T⁶, where T⁶ is

(i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl;

(heterocylco)alkyl, heteroaryl, or (heteroaryl)alkyl;

(ii) (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or

(iii) (iii) a group (i) or (ii) which is independently substituted by one or more (preferably 1 to 3) of the following groups (2) to (13) of the definition of T^{1-1c} , T^{2-2c} and T^{3-3c} ,

(2) -OH or -OT⁶,

(3) -SH or -ST⁶,

(4) $-C(O)_tH$, $-C(O)_tT^6$, or $-O-C(O)T^6$, where t is 1 or 2;

(5) $\text{--SO}_3\text{H}$, $-\text{S(O)}_t\text{T}^6$, or $\text{S(O)}_t\text{N(T)}^9\text{T}^6$,

30 (6) . halo,

(7) cyano,

- (8) nitro,
- (9) $-T^4-NT^7T^8$,
- (10) $-T^4-N(T^9)-T^5-NT^7T^8$,
- (11) $-T^4-N(T^{10})-T^5-T^6$,
- 5 (12) $-T^4-N(T^{10})-T^5-H$,
- (13) oxo,

T^4 and T^5 are each independently

- (1) a single bond,
- (2) $-T^{11}-S(O)_t-T^{12}-$,
- 10 (3) $-T^{11}-C(O)-T^{12}-$,
- (4) $-T^{11}-C(S)-T^{12}-$,
- (5) $-T^{11}-O-T^{12}-$,
- (6) $-T^{11}-S-T^{12}-$,
- (7) $-T^{11}-O-C(O)-T^{12}-$,
- 15 (8) $-T^{11}-C(O)-O-T^{12}-$,
- (9) $-T^{11}-C(=NT^{9a})-T^{12}-$, or
- (10) $-T^{11}-C(O)-C(O)-T^{12}-$

T^7 , T^8 , T^9 , T^{9a} and T^{10}

- (1) are each independently hydrogen or a group provided in the definition of T^6 ,
- 20 or
- (2) T^7 and T^8 may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T^{1-1c} , T^{2-2c} and T^{3-3c} , or
- (3) T^7 or T^8 , together with T^9 , may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T^{1-1c} , T^{2-2c} and T^{3-3c} , or
- (4) T^7 and T^8 or T^9 and T^{10} together with the nitrogen atom to which they are attached may combine to form a group $-N=CT^{13}T^{14}$ where T^{13} and T^{14} are each independently H or a group provided in the definition of T^6 ; and

T¹¹ and T¹² are each independently

- (1) a single bond,
- (2) alkylene,
- (3) alkenylene, or
- (4) alkynylene.

5

Preferred compounds of Formula I include those wherein:

Z is

- (a) halogen, alkoxy, haloalkyl, -NR³R⁴, -C(O)OR⁴, -C(O)NR³R⁴;
- (b) aryl or heteroaryl either of which may be optionally substituted with one or
10 more T^{1a}, T^{2a}, T^{3a} (especially cyano, optionally substituted alkyl,
(hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -SO_tT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸, or
-T⁴N(T¹⁰)-T⁵-T⁶);
- (c) optionally substituted alkyl (especially substituted with one or more -OH,
-CO_tH, -CO_tT⁶, -T⁴-NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-H, or ; -T⁴-N(T¹⁰)-T⁵-T⁶);

15 J is

- (a) H, or
- (b) alkyl or alkenyl either of which may be optionally substituted (especially with
one or more -OH, -OT⁶, -CO_tH, or -CO_tT⁶);

L is

- 20 (a) H;
- (b) halogen, alkoxy, haloalkyl, -NR⁵R⁶, -C(O)OR^{4b}, -C(O)NR⁵R⁶;
- (c) aryl or heteroaryl either of which may be optionally substituted with one or
more T^{1c}, T^{2c}, T^{3c} (especially cyano, optionally substituted alkyl,
(hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -SO_tT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸, or
25 -T⁴N(T¹⁰)-T⁵-T⁶); or
- (d) optionally substituted alkyl (especially substituted with one or more -OH,
-CO_tH, -CO_tT⁶, -T⁴-NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-H, or ; -T⁴-N(T¹⁰)-T⁵-T⁶);

R¹ is H or alkyl;

R² is

- (a) heteroaryl (more preferably thiazolyl or oxazolyl) optionally substituted with one to three groups T¹, T², T³, preferably including H, alkyl, haloalkyl, halo, heteroaryl, cyano, C(O)T⁶, OT⁶, -T⁴NT⁷T⁸;
- 5 (b) aryl substituted with one to three groups T¹, T², T³ (preferably including heteroaryl (preferably, imidazolyl, oxazolyl, or thiazolyl any of which may be further optionally substituted), cyano, C(O)T⁶, S(O)_tN(T⁹)T⁶, halo alkyl, and haloalkyl); or
- 10 (c) aryl fused to a heterocyclo ring (e.g., 2,3-dihydro-1H-indole bound through the aryl ring, quinolyl bound through the aryl ring (especially quinol-6-yl), quinazolinyl bound through the aryl ring (especially quinazolin-7-yl), cinnolinyl bound through the aryl ring (especially cinnolin-6-yl), isoquinolinyl bound through the aryl ring (especially isoquinol-6-yl), and phthalazinyl bound through the aryl ring (especially phthalazin-6-yl)) wherein the combined ring system may be optionally substituted with one 15 to three groups T¹, T², T³ (especially halo, OH, OT⁶, alkyl, -CO_tH, -CO_tT⁶, or -C(O)NT⁷T⁸);

R³ is H or optionally substituted alkyl (especially substituted with one or more -OH, or -OT⁶);

R⁴ is

- 20 (a) hydrogen;
- (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} (especially optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, 25 or heteroaryl);
- (c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} (especially optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, 30 -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl);

(d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} (especially optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO_tH, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl);

5 (e) alkyl optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} (especially -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or -T⁴-N(T¹⁰)-T⁵-T⁶);

10 (f) heterocyclo optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionaly subsituted heterocyclo, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸);

or R³ and R⁴ together with the nitrogen atom to which they are attached combine to form a 4 to 8-membered heterocyclo ring (especially pyrrolidinyl, piperadiny, 15 piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl)

optionally substituted with one to three groups T^{1a} , T^{2a} , T^{3a} (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionaly subsituted heterocyclo, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸);

20 R⁵ is hydrogen or alkyl;

R⁶ is

(a) hydrogen;

25 (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} (especially optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO_tH, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl);

30 (c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} (especially optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶,

-CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl);

(d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} (especially optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl);

(e) alkyl optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} (especially -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or -T⁴-N(T¹⁰)-T⁵-T⁶);

(f) heterocyclo optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionaly subsituted heterocyclo, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸);

or R⁵ and R⁶ together with the nitrogen atom to which they are attached combine to form a 4 to 8-membered heterocyclo ring (especially pyrrolidinyl, piperadiny, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl) optionally substituted with one to three groups T^{1c}, T^{2c}, T^{3c} (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionaly subsituted heterocyclo, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸).

More preferred compounds of the present invention include compounds wherein:

Z is

(a) halogen, alkoxy, haloalkyl, -NR³R⁴, -C(O)OR⁴, -C(O)NR³R⁴;

(b) aryl or heteroaryl either of which may be optionally substituted with one or more T^{1a}, T^{2a}, T^{3a} selected from cyano, optionally substituted alkyl, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -SO_tT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸, or -T⁴-N(T¹⁰)-T⁵-T⁶,

where

T⁴ is a bond or -C(O)-;

T⁵ is -C(O)-, or -C(O)O-;

T⁶ is alkyl or haloalkyl;

T⁷ and T⁸ are independently

5 H;

alkyl optiontionally substituted with cycloalkyl, heteroaryl,
hydroxy or -NT⁷T⁸;

cycloalkyl; or

aryl optionally substituted with halogen;

10 or T⁷ and T⁸ together with the nitrogen atom to which they are
attached combine to form a heterocyclo ring optionally
substituted with (hydroxy)alkyl, CO_tH or CO_tT⁶

T¹⁰ is hydrogen;

(c) alkyl optionally substituted with one or more -OH, -CO_tH, -CO_tT⁶,
-T⁴-NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-H, or ; -T⁴-N(T¹⁰)-T⁵-T⁶

15 where

T⁴ is -C(O)-;

T⁵ is -alkylene-O-;

T⁶ is alkyl;

20 T⁷ and T⁸ are independently H, alkyl, cycloalkyl, aryl, (aryl)alkyl
(optionally substituted as described in the definition of R⁴),
or heterocyclo (optionally substituted as described in the
definition of R³ and R⁴ combining to form a heterocyclo
ring); and

25 T¹⁰ is H;

J is

(a) H, or

(b) alkyl or alkenyl either of which may be optionally substituted with one or
more -OH, -OT⁶, -CO_tH, or -CO_tT⁶, where T⁶ is alkyl;

30 L is

(a) H;

(b) halogen, alkoxy, haloalkyl, -NR⁵R⁶, -C(O)OR^{4b}, -C(O)NR⁵R⁶;
 (c) aryl or heteroaryl either of which may be optionally substituted with one or
 more T^{1c}, T^{2c}, T^{3c} selected from cyano, optionally substituted alkyl
 especially substituted with CO_tH or CO_tT⁶), (hydroxy)alkyl, -OH, -OT⁶,

5 -ST⁶, -SO_tT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸, or -T⁴N(T¹⁰)-T⁵-T⁶,

where

T⁴ is a bond or -C(O)-;

T⁵ is -C(O)-, or -C(O)O-;

T⁶ is alkyl or haloalkyl;

10 T⁷ and T⁸ are independently

H;

alkyl optionionally substituted with cycloalkyl, heteroaryl,
 hydroxy or -NT⁷T⁸;

cycloalkyl; or

15 aryl optionally substituted with halogen;

or T⁷ and T⁸ together with the nitrogen atom to which they are
 attached combine to form a heterocyclo ring optionally
 substituted with (hydroxy)alkyl, CO_tH or CO_tT⁶

T¹⁰ is hydrogen;

20 (d) alkyl optionally substituted with one or more -OH, -CO_tH, -CO_tT⁶, -T⁴-NT⁷T⁸,
 -T⁴-N(T¹⁰)-T⁵-H, or ; -T⁴-N(T¹⁰)-T⁵-T⁶

where

T⁴ is -C(O)-;

T⁵ is -alkylene-O-;

25 T⁶ is alkyl;

T⁷ and T⁸ are independently H, alkyl, cycloalkyl, aryl, (aryl)alkyl
 (optionally substituted as described in the definition of R⁴),
 or heterocyclo (optionally substituted as described in the
 definition of R³ and R⁴ combining to form a heterocyclo
 ring); and

30 T¹⁰ is H;

R¹ is H or alkyl;

R² is

- (a) heteroaryl (more preferably thiazolyl or oxazolyl) optionally substituted with one to three groups T¹, T², T³, preferably including H, alkyl, haloalkyl, 5 halo, heteroaryl, cyano, C(O)_tT⁶, OT⁶, -T⁴NT⁷T⁸;
- (b) aryl substituted with one to three groups T¹, T², T³ (preferably including heteroaryl (preferably, imidazolyl, oxazolyl, or thiazolyl any of which may be further optionally substituted), cyano, C(O)_tT⁶, S(O)_tN(T⁹)T⁶, halo alkyl, and haloalkyl); or
- 10 (c) aryl fused to a heterocyclo ring (e.g., 2,3-dihydro-1H-indole bound through the aryl ring) wherein the combined ring system may be optionally substituted with one to three groups T¹, T², T³ (especially halo, OH, OT⁶, alkyl, -CO_tH, -CO_tT⁶, or -C(O)NT⁷T⁸);

R³ is H or optionally substituted alkyl (especially substituted with one or more -OH, or -OT⁶); 15

R⁴ is

- (a) hydrogen;
- (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, 20 halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl)

where

T⁴ is a bond, -SO₂-, or -C(O)-;

25 T⁵ is -SO₂-, or -alkylene-O-;

T⁶ is alkyl, or cycloalkyl;

T⁷ and T⁸ are independently H or alkyl; and

T⁹ and T¹⁰ are hydrogen;

- (c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶, 30

-ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸,
- $T^4\text{-}N(T^{10})\text{-}T^5\text{-}T^6$, heterocyclo, or heteroaryl)

where

T⁴ is a bond, -SO₂-; or -C(O)-;

5 T⁵ is -SO₂-; or -alkylene-O-;

T⁶ is alkyl, or cycloalkyl;

T⁷ and T⁸ are independently H or alkyl; and

T⁹ and T¹⁰ are hydrogen;

(d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -T⁴NT⁷T⁸, - $T^4\text{-}N(T^{10})\text{-}T^5\text{-}T^6$, heterocyclo, or heteroaryl)

where

15 T⁴ is a bond, -SO₂-; or -C(O)-;

T⁵ is -SO₂-; or -alkylene-O-;

T⁶ is alkyl, or cycloalkyl;

T⁷ and T⁸ are independently H or alkyl; and

T⁹ and T¹⁰ are hydrogen;

20 (e) alkyl optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or - $T^4\text{-}N(T^{10})\text{-}T^5\text{-}T^6$)

where

T⁴ is a bond;

25 T⁵ is -CO)-;

T⁶ is alkyl;

T⁷ and T⁸ are independently H or alkyl; and

T¹⁰ is hydrogen;

(f) heterocyclo optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl (especially substituted with -T⁴NT⁷T⁸), optionally substituted aryl (especially substituted with

halogen or haloalkyl), cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸)

where

T⁴ is a bond or -C(O)-;

5 T⁵ is -C(O)-, -SO₂-, or -alkylene-C(O)O-;

T⁶ is alkyl, alkoxy, or heteroaryl;

T⁷ and T⁸ are independently H, alkyl, or cycloalkyl;

or T⁷ and T⁸ together with the nitrogen atom to which they are attached combine to form a an optionally substituted 10 heterocyclo ring;

or R³ and R⁴ together with the nitrogen atom to which they are attached combine to form a heterocyclo ring selected from pyrrolidinyl, piperadiny, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), any of which are optionally independently substituted with one to three groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl (especially substituted with -T⁴NT⁷T⁸), 15 optionally substituted aryl (especially substituted with halogen or haloalkyl), cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸)

where

20 T⁴ is a bond or -C(O)-;

T⁵ is -C(O)-, -SO₂-, or -alkylene-C(O)O-;

T⁶ is alkyl, alkoxy, or heteroaryl;

T⁷ and T⁸ are independently H, alkyl, or cycloalkyl;

or T⁷ and T⁸ together with the nitrogen atom to which they are attached combine to form a an optionally substituted 25 heterocyclo ring;

R⁵ is hydrogen or alkyl;

R⁶ is

(a) hydrogen;

30 (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} selected from optionally substituted alkyl,

halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl)

where

- 5 T⁴ is a bond, -SO₂-, or -C(O)-;
- T⁵ is -SO₂-, or -alkylene-O-;
- T⁶ is alkyl, or cycloalkyl;
- T⁷ and T⁸ are independently H or alkyl; and
- T⁹ and T¹⁰ are hydrogen;
- 10 (c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl)
- 15 where
- T⁴ is a bond, -SO₂-, or -C(O)-;
- T⁵ is -SO₂-, or -alkylene-O-;
- T⁶ is alkyl, or cycloalkyl;
- T⁷ and T⁸ are independently H or alkyl; and
- T⁹ and T¹⁰ are hydrogen;
- 20 (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl)
- 25 where
- T⁴ is a bond, -SO₂-, or -C(O)-;
- T⁵ is -SO₂-, or -alkylene-O-;
- T⁶ is alkyl, or cycloalkyl;
- T⁷ and T⁸ are independently H or alkyl; and
- T⁹ and T¹⁰ are hydrogen;

(e) alkyl optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} selected from -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or -T⁴-N(T¹⁰)-T⁵-T⁶)

where

5 T⁴ is a bond;

 T⁵ is -CO)-;

 T⁶ is alkyl;

 T⁷ and T⁸ are independently H or alkyl; and

 T¹⁰ is hydrogen;

10 (f) heterocyclo optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} selected from optionally substituted alkyl (especially substituted with -T⁴NT⁷T⁸), optionally substituted aryl (especially substituted with halogen or haloalkyl), cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸)

15 where

 T⁴ is a bond or -C(O)-;

 T⁵ is -C(O)-, -SO₂-, or -alkylene-C(O)O-;

 T⁶ is alkyl, alkoxy, or heteroaryl;

 T⁷ and T⁸ are independently H, alkyl, or cycloalkyl;

20 or T⁷ and T⁸ together with the nitrogen atom to which they are attached combine to form a an optionally substituted heterocyclo ring;

or R⁵ and R⁶ together with the nitrogen atom to which they are attached combine to form a heterocyclo ring selected from pyrrolidinyl, piperadiny, piperazinyl,

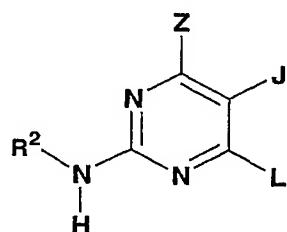
25 morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), any of which are optionally independently substituted with one to three groups T^{1a} , T^{2a} , T^{3a} selected from optionally substituted alkyl (especially substituted with -T⁴NT⁷T⁸), optionally substituted aryl (especially substituted with halogen or haloalkyl), cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸)

30 where

- T⁴ is a bond or -C(O)-;
- T⁵ is -C(O)-, -SO₂-, or -alkylene-C(O)O-;
- T⁶ is alkyl, alkoxy, or heteroaryl;
- T⁷ and T⁸ are independently H, alkyl, or cycloalkyl;
or T⁷ and T⁸ together with the nitrogen atom to which they are
attached combine to form a an optionally substituted
heterocyclo ring.

Preferred compounds of the present invention include compounds of Formula (II),

10

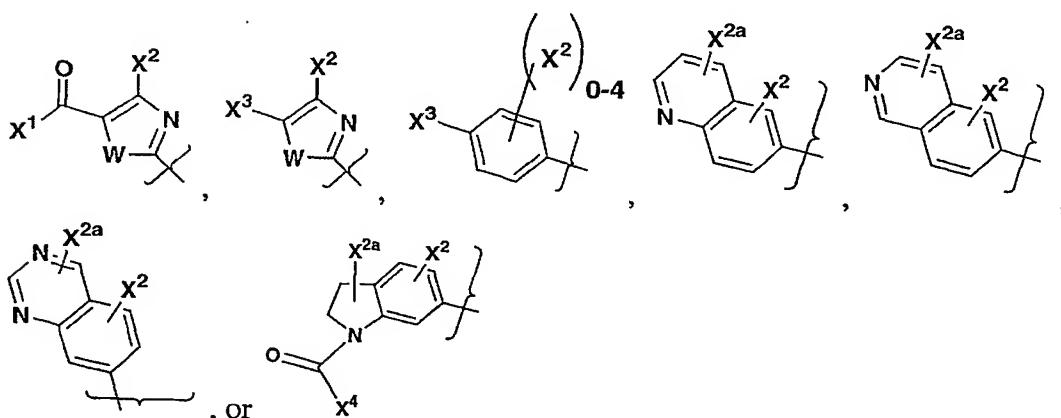


III

where:

Z, J and L are as described above (including preferred groups):

15 R^2 is



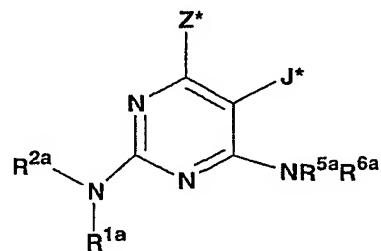
wherein:

20 W is O or S, more preferably S;
 X^1 is NHT⁸ or OT⁶.

X^2 and X^{2a} are independently hydrogen, halo, OT^6 , alkyl, or haloalkyl;
 X^3 is heteroaryl (preferably, pyrimidinyl, imidazolyl, oxazolyl, or thiazolyl any of which may be further optionally substituted), cyano, $C(O)_tT^6$, or $S(O)_tNT^7T^8$; and
 X^4 is alkyl, haloalkyl, NHT^8 or OT^6 .

5

Compounds within the scope of the Formulas I and II include dual PDE7-PDE4 inhibitors of the following Formula III:



III

10

wherein

R^{1a} is H or alkyl;

R^{2a} is optionally substituted heteroaryl;

15 Z^* is halogen, alkyl, substituted alkyl, haloalkyl, $NR^{3a}R^{4a}$, $-C(O)-N(T^{10})-T^5-H$, $-C(O)-N(T^{10})-T^5-T^6$, optionally substituted aryl or optionally substituted heteroaryl;

R^{3a} is hydrogen or alkyl;

R^{4a} is alkyl, alkoxy, optionally substituted (heteroaryl)alkyl, optionally substituted

20 heterocylo, optionally substituted (heterocyclo)alkyl, or (aryl)alkyl wherein the aryl group is substituted with one or two groups T^{1*} and T^{2*} and optionally further substituted with a group T^{3*} ;

or R^{3a} and R^{4a} together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring;

25 R^{5a} is optionally substituted (heteroaryl)alkyl, or (aryl)alkyl wherein the aryl group is substituted with one or two groups T^{1*} and T^{2*} and optionally further substituted with a group T^{3*} ;

- or R^{5a} and R^{6a} together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring;
- R^{6a} is hydrogen or alkyl;
- J* is hydrogen or alkyl;
- 5 T^{1*} and T^{2*} are independently alkoxy, alkoxycarbonyl, heteroaryl SO₃H or -SO₂R^{8a} where R^{8a} is alkyl, amino, alkylamino or dialkylamino;
- or T^{1*} and T^{2*} together with the aryl ring to which they are attached may combine to form a bicyclic ring (e.g., benzodioxole);
- T^{3*} is H, alkyl, halo, haloalkyl or cyano.

10

Preferred compounds within Formula III are those wherein:

- R^{1a} is H;
- R^{2a} is thiazolyl, oxazolyl, tetrahydroindolinyl, or isoxozolyl (preferably thiazolyl) any of which may be optionally substituted (preferably with one or more alkyl,
- 15 alkylcarbonyl or alkoxycarbonyl groups);
- Z* is halogen, alkyl, haloalkyl, NR^{3a}R^{4a}, -C(O)-N(T¹⁰)-T⁵-H, or -C(O)-N(T¹⁰)-T⁵-T⁶;
- R^{3a} is hydrogen;
- R^{4a} is alkyl, alkoxy, haloalkyl, or optionally substituted (heterocyclo)alkyl, especially where the heterocyclo ring is morpholinyl, pyrrolidinyl or tetrahydrofuranyl;
- 20 or R^{3a} and R^{4a} together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring, especially piperazine or piperidine or morpholine optionally substituted with one or more alkyl, (hydroxy)alkyl, hydroxy, -C(O)NT⁷T⁸, cyano, oxo, -CO_tH, or -CO_tT⁶;
- R^{5a} is
- a) (phenyl)alkyl where the phenyl group is substituted with one or two alkoxy, alkoxycarbonyl, heteroaryl (especially thiadiazolyl) or -SO₂R^{8a};
- b) optionally substituted (heteroaryl)alkyl; or
- c) optionally substituted (benzodioxole)alkyl, especially (1,3-benzodioxole)alkyl;
- 30 R^{6a} is hydrogen;

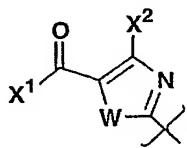
or R^{5a} and R^{6a} together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring, especially piperazine or piperidine or morpholine optionally substituted with one or more alkyl, (hydroxy)alkyl, hydroxy, -C(O)NT⁷T⁸, cyano, oxo, -CO_tH, or -CO_tT⁶; and

5 J* is hydrogen or alkyl.

More preferred compounds within Formula III are those wherein:

R^{1a} is hydrogen.

R^{2a} is



10 where W is O or S (preferably S), X¹ is alkoxy, and X² is alkyl;

Z* is halogen, haloalkyl, oxazolyl, phenyl (optionally substituted with heteroaryl, CO_tH or CO_tT⁶), -NR^{3a}R^{4a}, or -C(O)-N(H)-alkylene-COOH;

R^{3a} is hydrogen;

R^{4a} is alkyl, optionally substituted (morpholinyl)alkyl, optionally substituted (pyrrolidinyl)alkyl, or optionally substituted (tetrahydrofuranyl)alkyl;

15 or R^{3a} and R^{4a} together with the nitrogen atom to which they are attached may combine to form a piperazine, piperadine or morpholine ring optionally substituted with one or more alkyl, (hydroxy)alkyl, hydroxy, -C(O)NH₂, cyano, oxo, or -CO_talkyl;

20 R^{5a} is

a) (phenyl)alkyl where the phenyl group is substituted with one or more alkoxy, alkoxy carbonyl, heteroaryl (especially thiadiazolyl) or -SO₂R^{8a};

b) (tetrazolyl)alkyl, or (pyridyl)alkyl;

c) optionally substituted (benzodioxole)alkyl, especially (1,3-benzodioxole)alkyl;

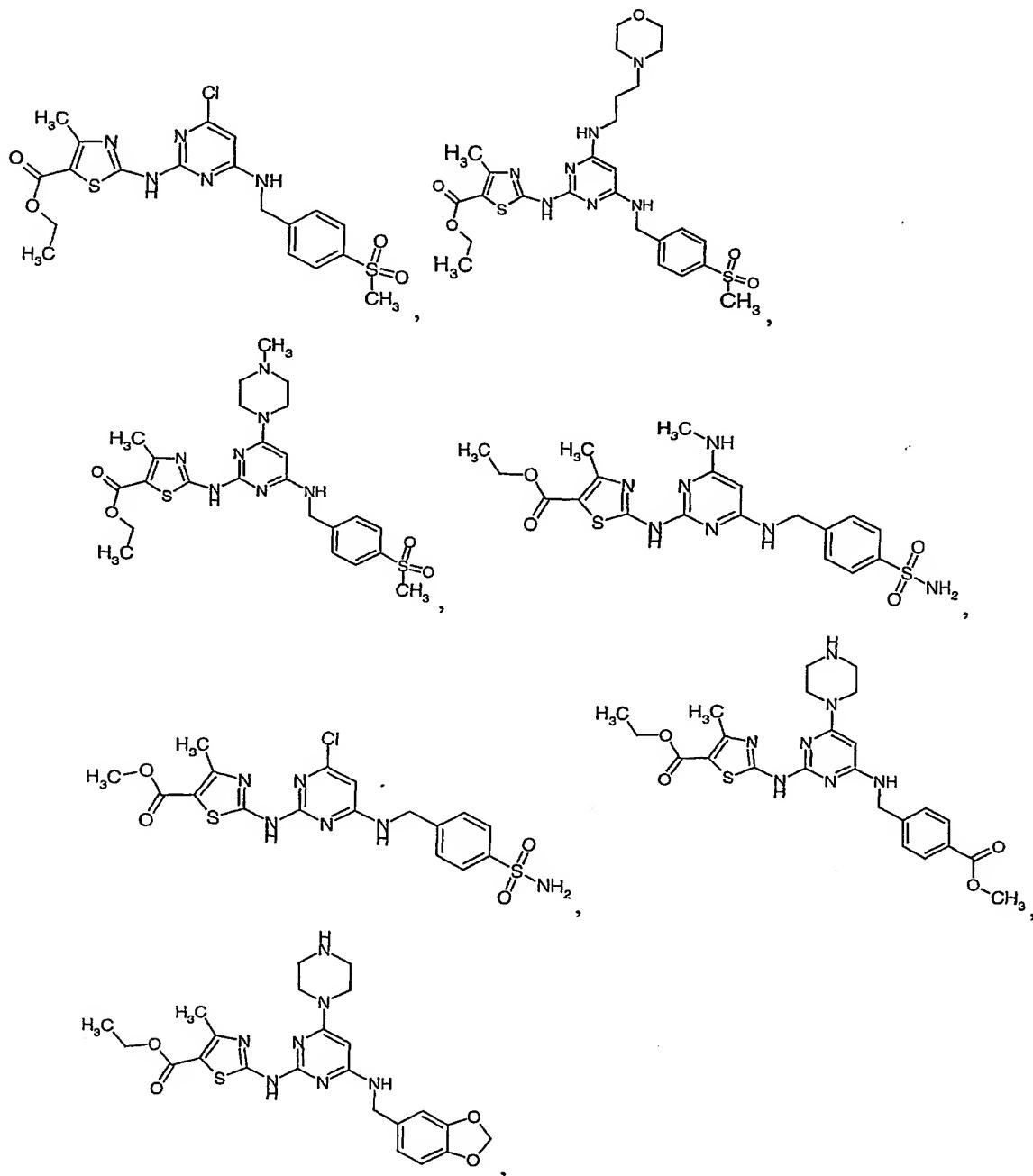
25 R^{6a} is hydrogen;

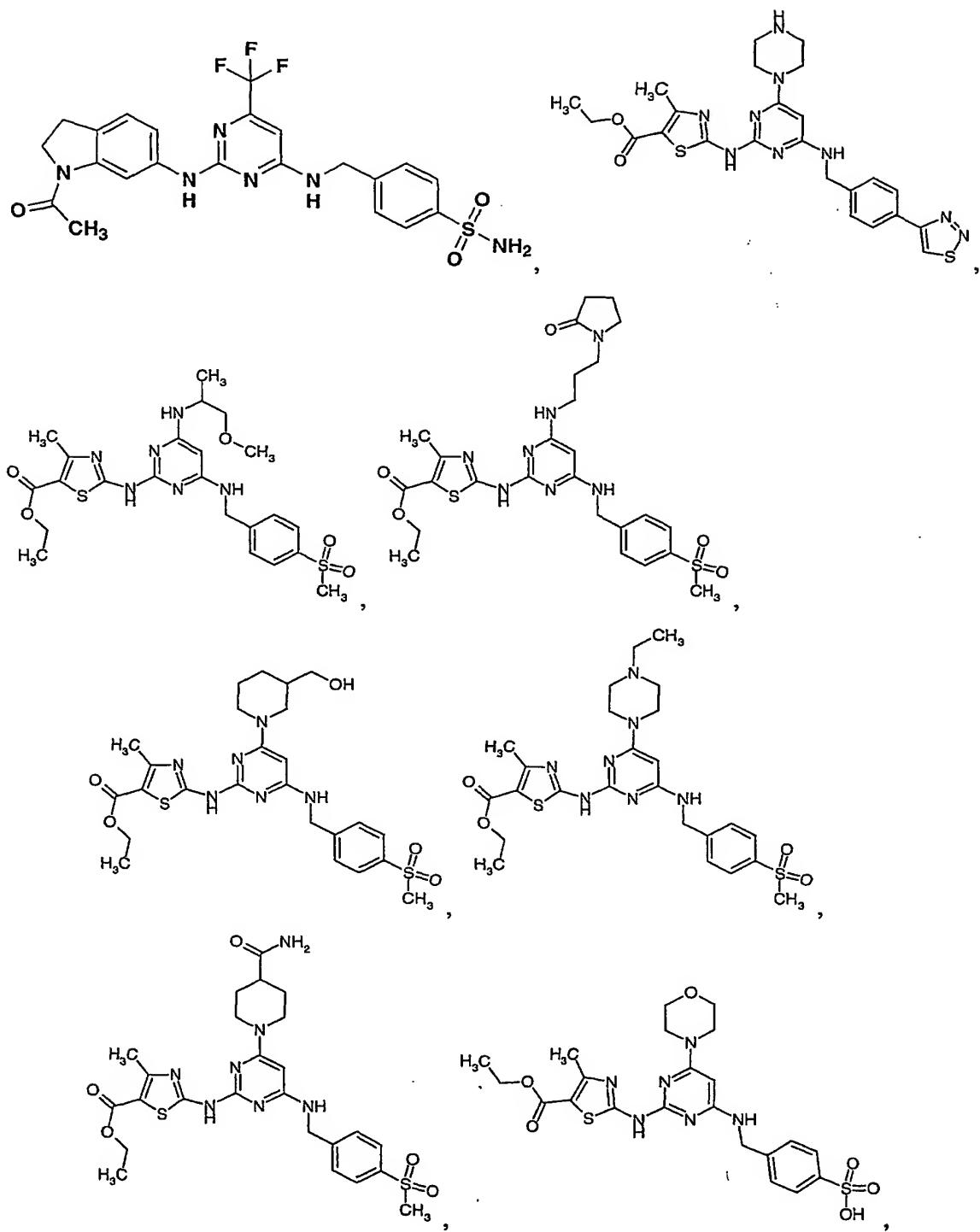
or R^{5a} and R^{6a} together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring, especially piperazine or

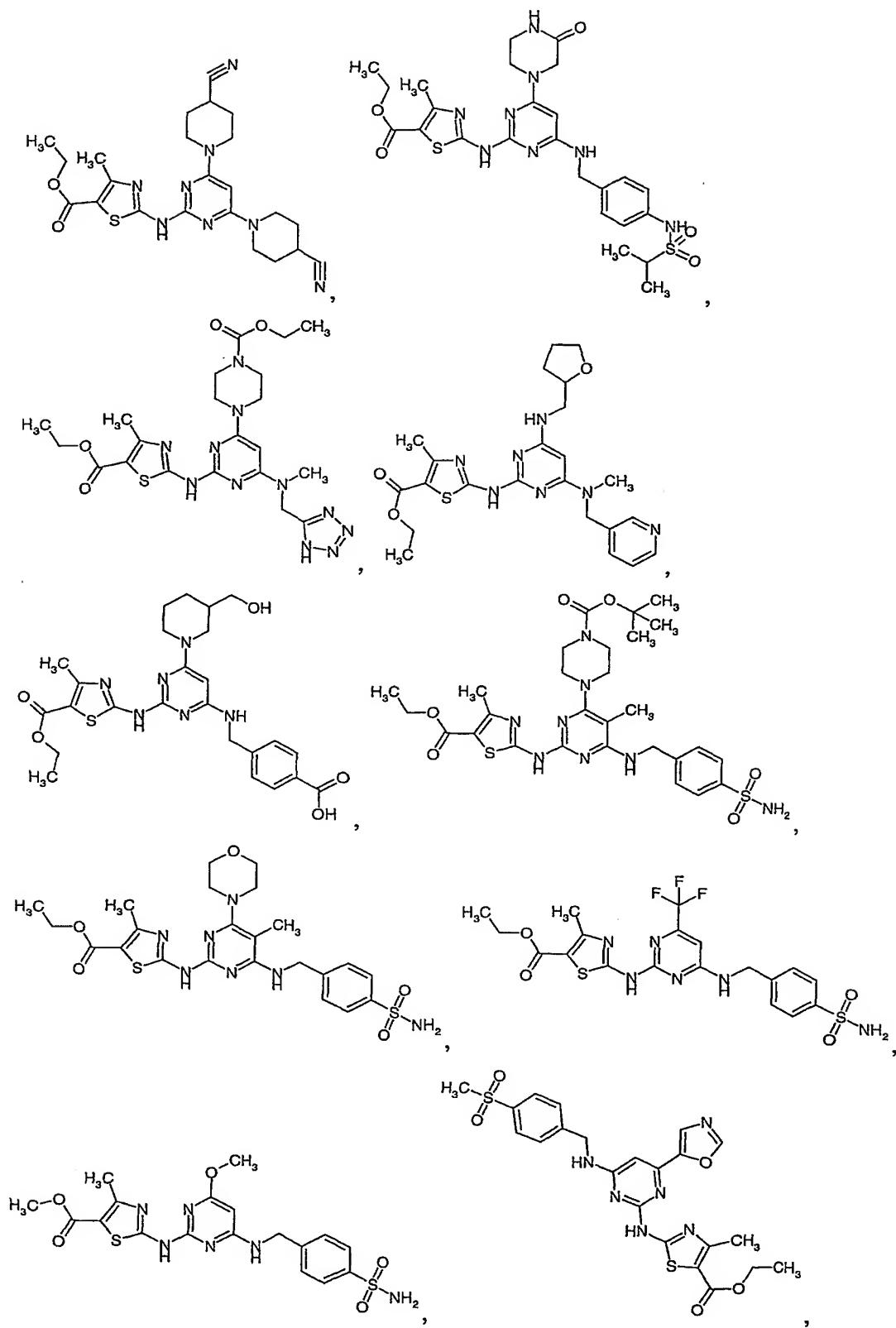
piperidine or morpholine optionally substituted with one or more alkyl, (hydroxy)alkyl, hydroxy, -C(O)NH₂, cyano, oxo, or -CO_talkyl; and J* is hydrogen or alkyl.

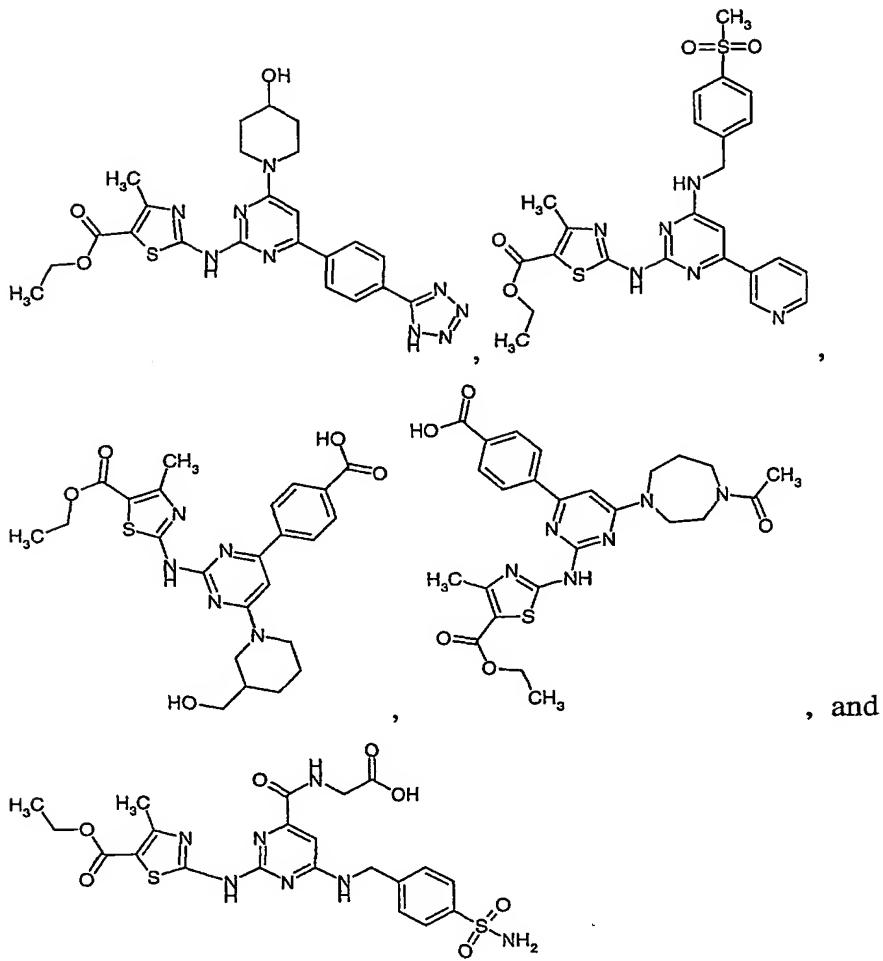
5

Preferred compounds within the scope of formula III include:









5 The following are definitions of the terms as used throughout this specification and claims. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

10 The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, etc. Lower alkyl groups, that is, alkyl groups of 1 to 6 carbon atoms, are generally most preferred.

15 The term "substituted alkyl" refers to alkyl groups substituted with one or more groups listed in the definition of T¹, T² and T³, preferably selected from halo, cyano, O-R₇, S-R₇, NR₈R₉, nitro, cycloalkyl, substituted cycloalkyl, oxo, aryl, substituted aryl,

heterocyclo, heteroaryl, CO₂R₇, S(O)R₇, SO₂R₇, SO₃R₇, SO₂NR₈R₉, C(O)NR₈R₉, C(O)alkyl, and C(O)H.

The term "alkylene" refers to a straight chain bridge of 1 to 4 carbon atoms connected by single bonds (e.g., -(CH₂)_x- wherein x is 1 to 5), which may be substituted 5 with one or more groups listed in the definition of T¹, T² and T³.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, preferably 2 to 4 carbon atoms, and at least one double carbon to carbon bond (either cis or trans), such as ethenyl.

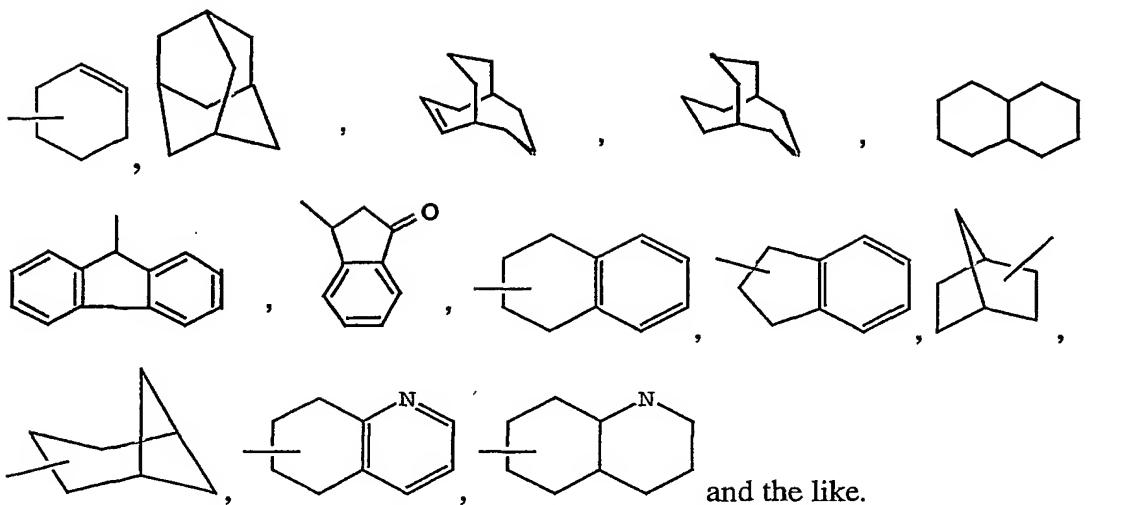
The term "substituted alkenyl" refers to an alkenyl group as defined above 10 substituted with one or more groups listed in the definition of T¹, T² and T³, preferably selected from halo, cyano, O-R₇, S-R₇, NR₈R₉, nitro, cycloalkyl, substituted cycloalkyl, oxo, aryl, substituted aryl, heterocyclo, heteroaryl, CO₂R₇, S(O)R₇, SO₂R₇, SO₃R₇, SO₂NR₈R₉, C(O)NR₈R₉, C(O)alkyl, and C(O)H.

The term "alkynyl" refers to straight or branched chain hydrocarbon group having 15 2 to 12 carbon atoms and one, two or three triple bonds, preferably 2 to 6 carbon atoms and one triple bond.

The term "substituted alkynyl" refers to an alkynyl group as defined above substituted with one or more groups listed in the definition of T¹, T² and T³, preferably 20 selected from halo, cyano, O-R₇, S-R₇, NR₈R₉, nitro, cycloalkyl, substituted cycloalkyl, oxo, aryl, substituted aryl, heterocyclo, heteroaryl, CO₂R₇, S(O)R₇, SO₂R₇, SO₃R₇, SO₂NR₈R₉, C(O)NR₈R₉, C(O)alkyl, and C(O)H.

The term "halo" refers to chloro, bromo, fluoro, and iodo.

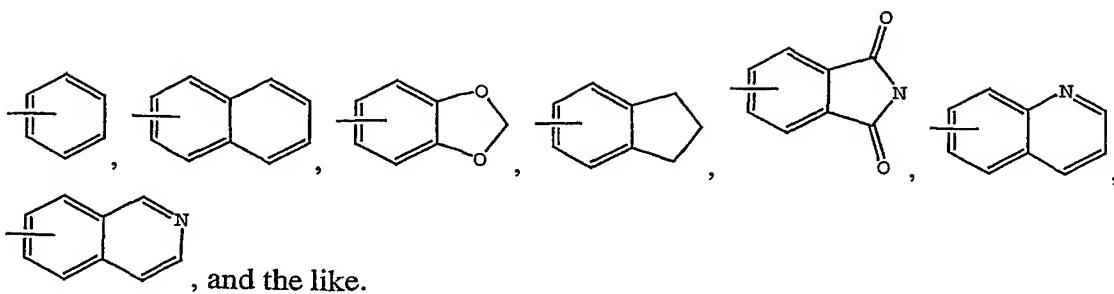
The term "cycloalkyl" refers to saturated and partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including 25 monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 7 carbons, forming the ring and which may be fused to 1 or 2 aromatic or heterocyclo rings, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, cyclohexenyl,



The term "substituted cycloalkyl" refers to such cycloalkyl group as defined above

- 5 substituted with one or more groups listed in the definition of T^1 , T^2 and T^3 , preferably selected from halogen, nitro, alkyl, substituted alkyl, alkenyl, cyano, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo, heteroaryl, oxo, OR_7 , CO_2R_7 , $C(O)NR_8R_9$, $OC(O)R_7$, $OC(O)OR_7$, $OC(O)NR_8R_9$, $OCH_2CO_2R_7$, $C(O)R_7$, NR_8R_9 , $NR_{10}C(O)R_7$, $NR_{10}C(O)OR_7$, $NR_{10}C(O)C(O)OR_7$, $NR_{10}C(O)C(O)NR_8R_9$,
- 10 $NR_{10}C(O)C(O)\text{alkyl}$, $NR_{10}C(NCN)OR_7$, $NR_{10}C(O)NR_8R_9$, $NR_{10}C(NCN)NR_8R_9$, $NR_{10}C(NR_{11})NR_8R_9$, $NR_{10}SO_2NR_8R_9$, $NR_{10}SO_2R_7$, SR_7 , $S(O)R_7$, SO_2R_7 , SO_3R_7 , $SO_2NR_8R_9$, $NHOR_7$, $NR_{10}NR_8R_9$, $N(COR_7)OR_{10}$, $N(CO_2R_7)OR_{10}$, $C(O)NR_{10}(CR_{12}R_{13})_rR_7$, $CO(CR_{12}R_{13})pO(CR_{14}R_{15})qCO_2R_7$, $CO(CR_{12}R_{13})rOR_7$, $CO(CR_{12}R_{13})pO(CR_{14}R_{15})qR_7$, $CO(CR_{12}R_{13})rNR_8R_9$, $OC(O)O(CR_{12}R_{13})mNR_8R_9$,
- 15 $OC(O)N(CR_{12}R_{13})rR_7$, $O(CR_{12}R_{13})mNR_8R_9$, $NR_{10}C(O)(CR_{12}R_{13})rR_7$, $NR_{10}C(O)(CR_{12}R_{13})rOR_7$, $NR_{10}C(=NC)(CR_{12}R_{13})rR_7$, $NR_{10}CO(CR_{12}R_{13})rNR_8R_9$, $NR_{10}(CR_{12}R_{13})mOR_7$, $NR_{10}(CR_{12}R_{13})rCO_2R_7$, $NR_{10}(CR_{12}R_{13})mNR_8R_9$, $NR_{10}(CR_{12}R_{13})nSO_2(CR_{14}R_{15})qR_7$, $CONR_{10}(CR_{12}R_{13})nSO_2(CR_{14}R_{15})qR_7$, $SO_2NR_{10}(CR_{12}R_{13})nCO(CR_{14}R_{15})qR_7$, and $SO_2NR_{10}(CR_{12}R_{13})mOR_7$.

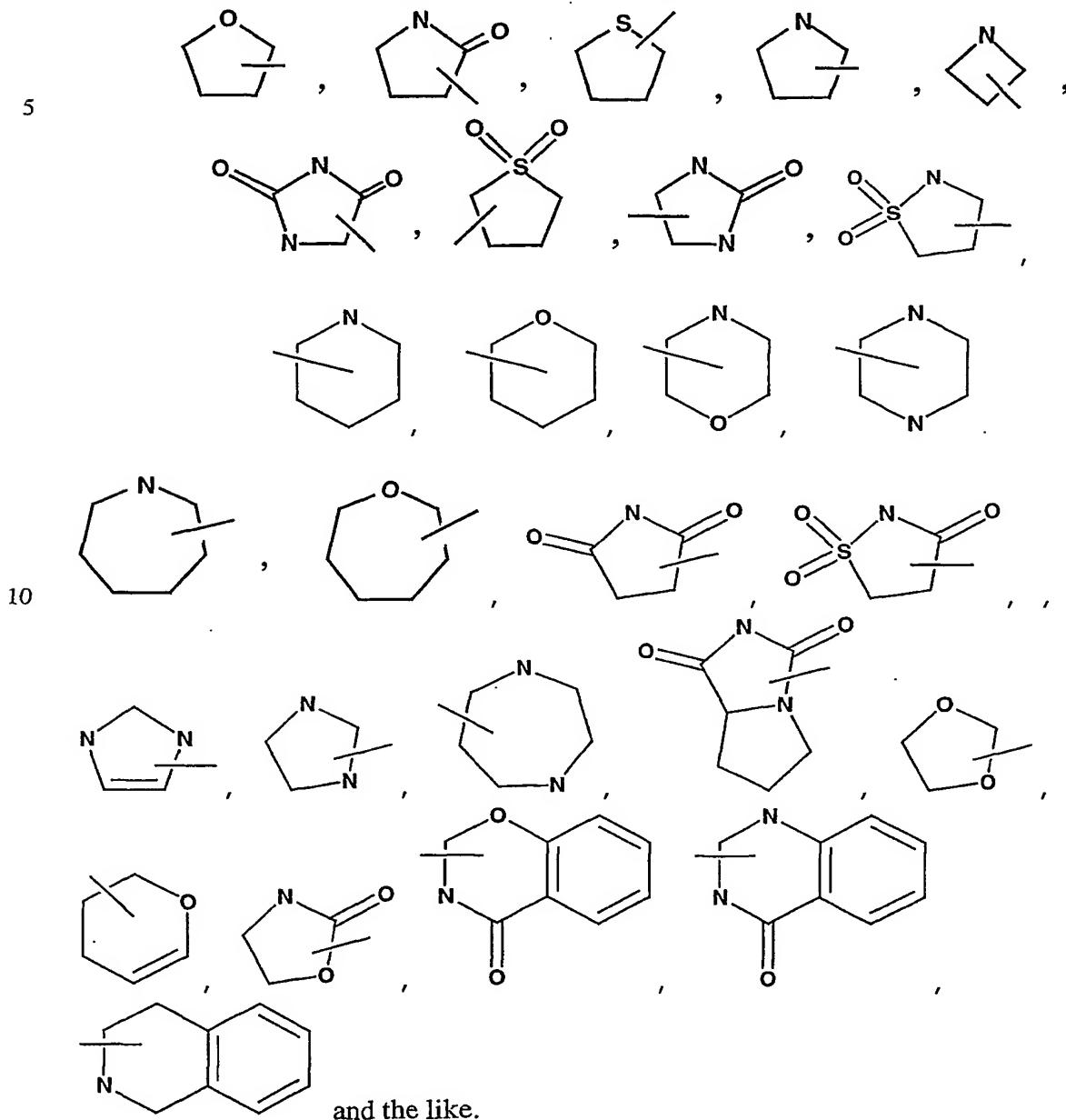
- 20 The terms "ar" or "aryl" refer to aromatic homocyclic (i.e., hydrocarbon) mono-, bi- or tricyclic ring-containing groups preferably having 6 to 12 members such as phenyl, naphthyl and biphenyl, as well as such rings fused to a cycloalkyl, cycloalkenyl, heterocyclo, or heteroaryl ring. Examples include:



The term "substituted aryl" refers to such aryl groups as defined above substituted
 5 with one or more groups listed in the definition of T¹, T² and T³, preferably selected from
 halogen, nitro, alkyl, substituted alkyl, alkenyl, cyano, cycloalkyl, substituted cycloalkyl,
 aryl, substituted aryl, heterocyclo, heteroaryl, OR₇, CO₂R₇, C(O)NR₈R₉, OC(O)R₇,
 OC(O)OR₇, OC(O)NR₈R₉, OCH₂CO₂R₇, C(O)R₇, NR₈R₉, NR₁₀C(O)R₇, NR₁₀C(O)OR₇,
 NR₁₀C(O)C(O)OR₇, NR₁₀C(O)C(O)NR₈R₉, NR₁₀C(O)C(O)alkyl, NR₁₀C(NCN)OR₇,
 10 NR₁₀C(O)NR₈R₉, NR₁₀C(NCN)NR₈R₉, NR₁₀C(NR₁₁)NR₈R₉, NR₁₀SO₂NR₈R₉,
 NR₁₀SO₂R₇, SR₇, S(O)R₇, SO₂R₇, SO₃R₇, SO₂NR₈R₉, NHOR₇, NR₁₀NR₈R₉,
 N(COR₇)OR₁₀, N(CO₂R₇)OR₁₀, C(O)NR₁₀(CR₁₂R₁₃)_rR₇,
 CO(CR₁₂R₁₃)pO(CR₁₄R₁₅)qCO₂R₇, CO(CR₁₂R₁₃)rOR₇, CO(CR₁₂R₁₃)pO(CR₁₄R₁₅)qR₇,
 CO(CR₁₂R₁₃)rNR₈R₉, OC(O)O(CR₁₂R₁₃)mNR₈R₉, OC(O)N(CR₁₂R₁₃)rR₇,
 15 O(CR₁₂R₁₃)mNR₈R₉, NR₁₀C(O)(CR₁₂R₁₃)rR₇, NR₁₀C(O)(CR₁₂R₁₃)rOR₇,
 NR₁₀C(=NC)(CR₁₂R₁₃)rR₇, NR₁₀CO(CR₁₂R₁₃)rNR₈R₉, NR₁₀(CR₁₂R₁₃)mOR₇,
 NR₁₀(CR₁₂R₁₃)rCO₂R₇, NR₁₀(CR₁₂R₁₃)mNR₈R₉, NR₁₀(CR₁₂R₁₃)nSO₂(CR₁₄R₁₅)qR₇,
 CONR₁₀(CR₁₂R₁₃)nSO₂(CR₁₄R₁₅)qR₇,
 20 SO₂NR₁₀(CR₁₂R₁₃)nCO(CR₁₄R₁₅)qR₇, and SO₂NR₁₀(CR₁₂R₁₃)mOR₇ as well as
 pentafluorophenyl.

The terms "heterocycle", "heterocyclic", "heterocyclic group" or "heterocyclo"
 refer to fully saturated or partially unsaturated cyclic groups (for example, 3 to 13
 member monocyclic, 7 to 17 member bicyclic, or 10 to 20 member tricyclic ring systems,
 preferably containing a total of 3 to 10 ring atoms) which have at least one heteroatom in
 25 at least one carbon atom-containing ring. Each ring of the heterocyclic group containing
 a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen
 atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be

oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. The rings of multi-ring heterocycles may be either fused, bridged and/or joined through one or more spiro unions. Exemplary heterocyclic groups include



15 The terms "substituted heterocycle" or "substituted heterocyclo" and the like refer to such heterocylo groups as defined above substituted with one or more groups listed in

the definition of T¹, T² and T³, preferably selected from halogen, nitro, alkyl, substituted alkyl, alkenyl, cyano, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo, heteroaryl, oxo, OR₇, CO₂R₇, C(O)NR₈R₉, OC(O)R₇, OC(O)OR₇, OC(O)NR₈R₉, OCH₂CO₂R₇, C(O)R₇, NR₈R₉, NR₁₀C(O)R₇, NR₁₀C(O)OR₇,

5 NR₁₀C(O)C(O)OR₇, NR₁₀C(O)C(O)NR₈R₉, NR₁₀C(O)C(O)alkyl, NR₁₀C(NCN)OR₇, NR₁₀C(O)NR₈R₉, NR₁₀C(NCN)NR₈R₉, NR₁₀C(NR₁₁)NR₈R₉, NR₁₀SO₂NR₈R₉, NR₁₀SO₂R₇, SR₇, S(O)R₇, SO₂R₇, SO₃R₇, SO₂NR₈R₉, NHOR₇, NR₁₀NR₈R₉, N(COR₇)OR₁₀, N(CO₂R₇)OR₁₀, C(O)NR₁₀(CR₁₂R₁₃)R₇,

10 CO(CR₁₂R₁₃)pO(CR₁₄R₁₅)qCO₂R₇, CO(CR₁₂R₁₃)rOR₇, CO(CR₁₂R₁₃)pO(CR₁₄R₁₅)qR₇, CO(CR₁₂R₁₃)rNR₈R₉, OC(O)O(CR₁₂R₁₃)mNR₈R₉, OC(O)N(CR₁₂R₁₃)rR₇,

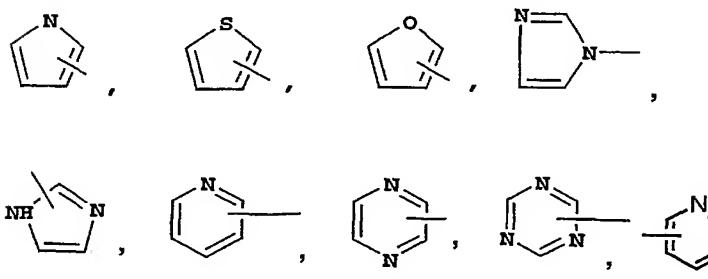
O(CR₁₂R₁₃)mNR₈R₉, NR₁₀C(O)(CR₁₂R₁₃)rR₇, NR₁₀C(O)(CR₁₂R₁₃)rOR₇, NR₁₀C(=NC)(CR₁₂R₁₃)rR₇, NR₁₀CO(CR₁₂R₁₃)rNR₈R₉, NR₁₀(CR₁₂R₁₃)mOR₇,

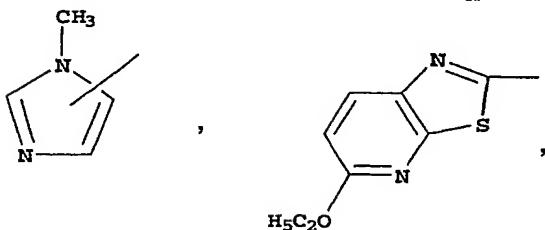
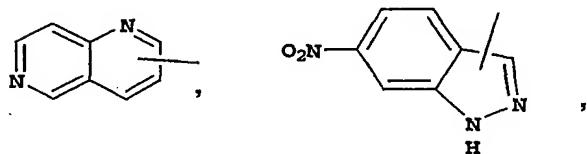
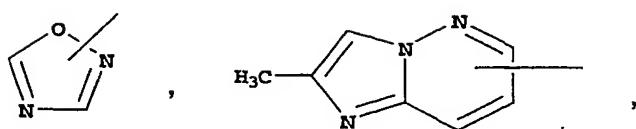
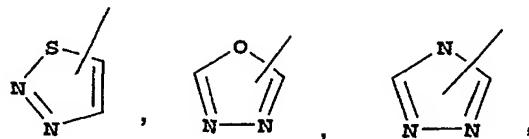
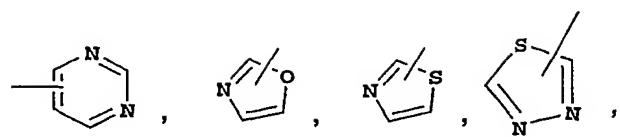
15 NR₁₀(CR₁₂R₁₃)rCO₂R₇, NR₁₀(CR₁₂R₁₃)mNR₈R₉, NR₁₀(CR₁₂R₁₃)nSO₂(CR₁₄R₁₅)qR₇, CONR₁₀(CR₁₂R₁₃)nSO₂(CR₁₄R₁₅)qR₇,

SO₂NR₁₀(CR₁₂R₁₃)nCO(CR₁₄R₁₅)qR₇, and SO₂NR₁₀(CR₁₂R₁₃)mOR₇.

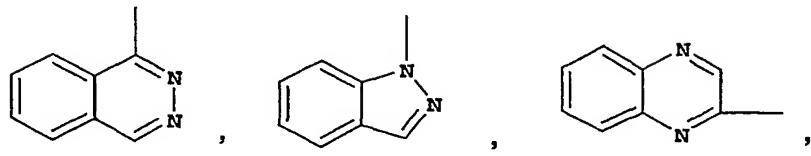
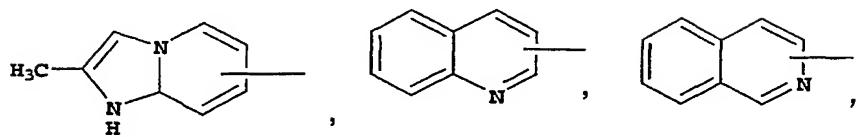
The term "heteroaryl" as used herein alone or as part of another group refers to a 5- 6- or 7- membered aromatic rings containing from 1 to 4 nitrogen atoms and/or 1 or 2 oxygen or sulfur atoms provided that the ring contains at least 1 carbon atom and no more than 4 heteroatoms. The heteroaryl ring is linked through an available carbon or nitrogen atom. Also included within the definition of heteroaryl are such rings fused to a cycloalkyl, aryl, cycloheteroalkyl, or another heteroaryl ring. One, two, or three available carbon or nitrogen atoms in the heteroaryl ring can be optionally substituted with substituents listed in the description of T₁, T₂ and T₃. Also an available nitrogen or sulfur atom in the heteroaryl ring can be oxidized. Examples of heteroaryl rings include

25

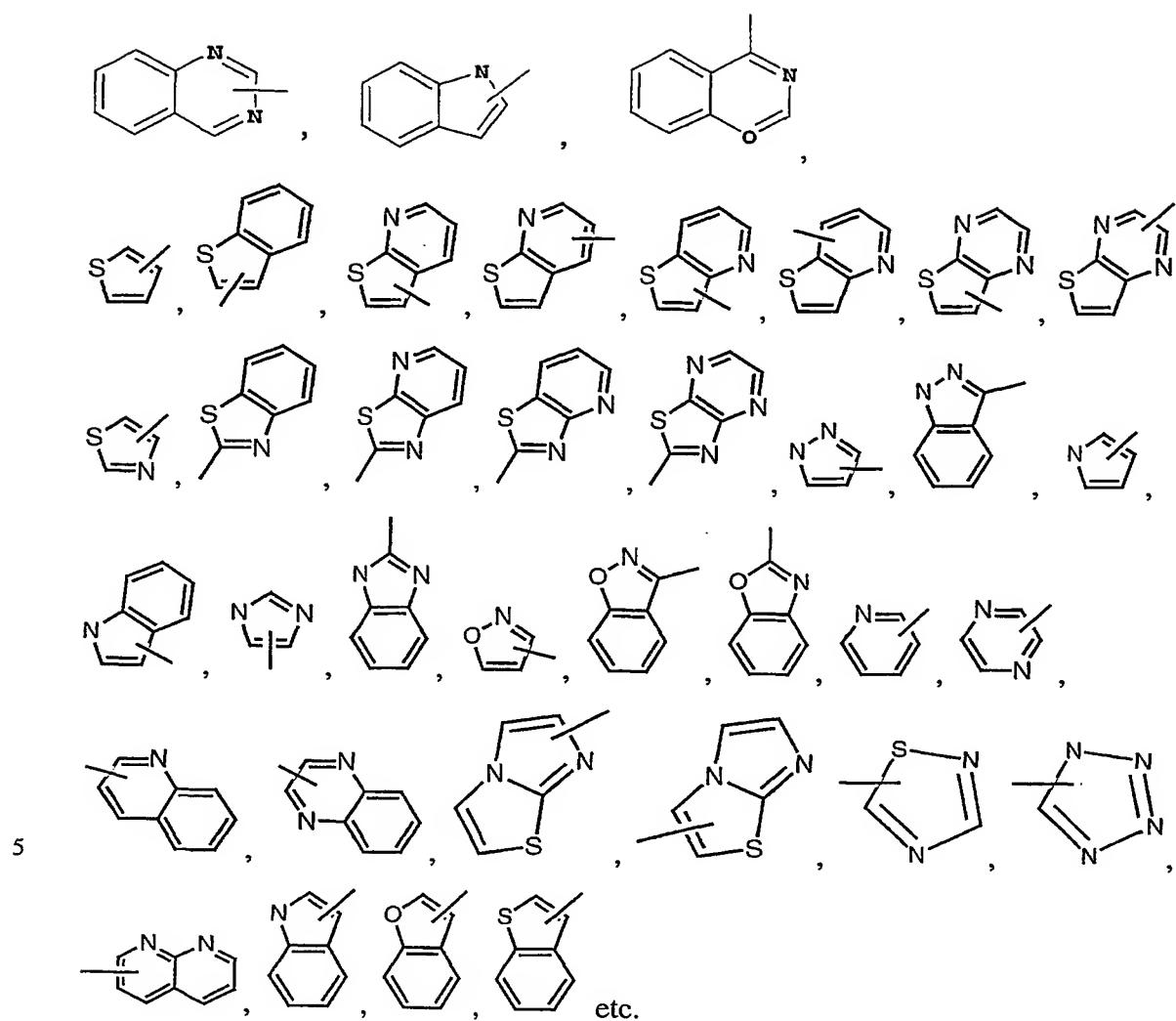




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5

The term "substituted heteroaryl" refers to such heteroaryl groups as defined above substituted on any available atom with one or more groups listed in the definition of T¹, T² and T³, preferably selected from" refers to such heterocyclo groups as defined above substituted with one or more groups listed in the definition of T¹, T² and T³, preferably selected from halogen, nitro, alkyl, substituted alkyl, alkenyl, cyano, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo, heteroaryl, OR₇, CO₂R₇, C(O)NR₈R₉, OC(O)R₇, OC(O)OR₇, OC(O)NR₈R₉, OCH₂CO₂R₇, C(O)R₇, NR₈R₉, NR₁₀C(O)R₇, NR₁₀C(O)OR₇, NR₁₀C(O)C(O)OR₇, NR₁₀C(O)C(O)NR₈R₉, NR₁₀C(O)C(O)alkyl, NR₁₀C(NCN)OR₇, NR₁₀C(O)NR₈R₉, NR₁₀C(NCN)NR₈R₉, NR₁₀C(NR₁₁)NR₈R₉, NR₁₀SO₂NR₈R₉, NR₁₀SO₂R₇, SR₇, S(O)R₇, SO₂R₇, SO₃R₇, SO₂NR₈R₉, NHOR₇, NR₁₀NR₈R₉, N(COR₇)OR₁₀, N(CO₂R₇)OR₁₀,

C(O)NR₁₀(CR₁₂R₁₃)_rR₇, CO(CR₁₂R₁₃)pO(CR₁₄R₁₅)qCO₂R₇, CO(CR₁₂R₁₃)rOR₇,
 CO(CR₁₂R₁₃)pO(CR₁₄R₁₅)qR₇, CO(CR₁₂R₁₃)rNR₈R₉, OC(O)O(CR₁₂R₁₃)mNR₈R₉,
 OC(O)N(CR₁₂R₁₃)rR₇, O(CR₁₂R₁₃)mNR₈R₉, NR₁₀C(O)(CR₁₂R₁₃)rR₇,
 NR₁₀C(O)(CR₁₂R₁₃)rOR₇, NR₁₀C(=NC)(CR₁₂R₁₃)rR₇, NR₁₀CO(CR₁₂R₁₃)rNR₈R₉,
 5 NR₁₀(CR₁₂R₁₃)mOR₇, NR₁₀(CR₁₂R₁₃)rCO₂R₇, NR₁₀(CR₁₂R₁₃)mNR₈R₉,
 NR₁₀(CR₁₂R₁₃)nSO₂(CR₁₄R₁₅)qR₇, CONR₁₀(CR₁₂R₁₃)nSO₂(CR₁₄R₁₅)qR₇,
 SO₂NR₁₀(CR₁₂R₁₃)nCO(CR₁₄R₁₅)qR₇, and SO₂NR₁₀(CR₁₂R₁₃)mOR₇.

R₇, R₁₀, and R₁₁, are independently selected from the group consisting of
 10 hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, substituted cycloalkyl,
 C(O)alkyl, C(O)substituted alkyl, C(O)cycloalkyl, C(O) substituted cycloalkyl, C(O)aryl,
 C(O)substituted aryl, C(O)Oalkyl, C(O)Osustituted alkyl, C(O)heterocyclo,
 C(O)heteroaryl, aryl, substituted aryl, heterocyclo and heteroaryl.

R₈ and R₉ are independently selected from the group consisting of hydrogen,
 alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, alkynyl, C(O)alkyl,
 15 C(O)substituted alkyl, C(O)cycloalkyl, C(O)substituted cycloalkyl, C(O)aryl,
 C(O)substituted aryl, C(O)Oalkyl, C(O)Osustituted alkyl, C(O)heterocyclo,
 C(O)heteroaryl, S(O)₂alkyl, S(O)₂substituted alkyl, S(O)₂cycloalkyl, S(O)₂substituted
 cycloalkyl, S(O)₂aryl, S(O)₂substituted aryl, S(O)₂heterocyclo, S(O)₂heteroaryl, aryl,
 substituted aryl, heterocyclo, and heteroaryl or R₈ and R₉ taken together with the nitrogen
 20 atom to which they are attached complete a heterocyclo or heteroaryl ring.

R₁₂ and R₁₄ are independently selected from hydrogen and alkyl or 1 to 4 carbons.

R₁₃ and R₁₅ are independently selected from hydrogen, alkyl of 1 to 4 carbons,
 and substituted alkyl or 1 to 4 carbons.

n is zero or an integer from 1 to 4.

25 m is an integer from 2 to 6.

p is an integer from 1 to 3.

q is zero or an integer from 1 to 3.

r is zero or an integer from 1 to 6.

T¹, T², and T³ are are each independently

30 (1) hydrogen or T⁶, where T⁶ is

- (i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl;
- 5 (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or
- (iii) a group (i) or (ii) which is independently substituted by one or more (preferably 1 to 3) of the following groups (2) to (13) of the definition of T¹, T² and T³;

- 10 (2) -OH or -OT⁶,
- (3) -SH or -ST⁶,
- (4) -C(O)_tH, -C(O)_tT⁶, or -O-C(O)T⁶, where t is 1 or 2;
- (5) -SO₃H, -S(O)_tT⁶, or S(O)_tN(T⁹)T⁶,
- (6) halo,
- 15 (7) cyano,
- (8) nitro,
- (9) -T⁴-NT⁷T⁸,
- (10) -T⁴-N(T⁹)-T⁵-NT⁷T⁸,
- (11) -T⁴-N(T¹⁰)-T⁵-T⁶,
- 20 (12) -T⁴-N(T¹⁰)-T⁵-H,
- (13) oxo,

T⁴ and T⁵ are each independently

- (1) a single bond,
- (2) -T¹¹-S(O)_t-T¹²-,
- 25 (3) -T¹¹-C(O)-T¹²-,
- (4) -T¹¹-C(S)-T¹²-,
- (5) -T¹¹-O-T¹²-,
- (6) -T¹¹-S-T¹²-,
- (7) -T¹¹-O-C(O)-T¹²-,
- 30 (8) -T¹¹-C(O)-O-T¹²-,
- (9) -T¹¹-C(=NT^{9a})-T¹²-, or

(10) $-T^{11}-C(O)-C(O)-T^{12}-$
 T^7, T^8, T^9, T^{9a} and T^{10}

- (1) are each independently hydrogen or a group provided in the definition of T^6 ,
or
5 (2) T^7 and T^8 may together be alkylene or alkenylene, completing a 3- to 8-
membered saturated or unsaturated ring together with the atoms to which
they are attached, which ring is unsubstituted or substituted with one or more
groups listed in the description of T^1 , T^2 and T^3 , or
10 (3) T^7 or T^8 , together with T^9 , may be alkylene or alkenylene completing a 3- to
8-membered saturated or unsaturated ring together with the nitrogen atoms to
which they are attached, which ring is unsubstituted or substituted with one
or more groups listed in the description of T^1 , T^2 and T^3 , or
15 (4) T^7 and T^8 or T^9 and T^{10} together with the nitrogen atom to which they are
attached may combine to form a group $-N=CT^{13}T^{14}$ where T^{13} and T^{14} are each
independently H or a group provided in the definition of T^6 ; and
20 T^{11} and T^{12} are each independently
(1) a single bond,
(2) alkylene,
(3) alkenylene, or
(4) alkynylene.

“T cell-mediated diseases” refers to any disorder or disease state in which modulation of the activity of T cells is implicated in a process which results in either a pathophysiological state or a process where the normal function of T cells is intended to be suppressed for therapeutic benefit. Examples of T cell mediated disorders include
25 transplant rejection, graft versus host disease, and autoimmune disorders, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, T-cell mediated hypersensitivity diseases, ischemic or reperfusion injury, and T-cell proliferative disorders.

PDE7 inhibitors in accordance with the present invention are employed,
30 typically in the form of a pharmaceutical composition including a pharmaceutically acceptable carrier for the treatment of T-cell mediated disease. The compounds

employed for this purpose are typically administered in an amount from about 0.01 to 100 mg/kg/day.

The pharmaceutical compositions comprising at least one PDE7 inhibitor may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The PDE7 inhibitors may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds may also be administered in the form of liposomes.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The present compounds may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the

present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound employed in the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.01 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the

metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and
5 domestic animals such as dogs, cats and the like, subject to inflammatory, immunological, or respiratory cell-associated disorders.

PDE7 inhibitors for use in the treatment of various T-cell mediated diseases are those covered by Formula I

10 Compounds of Formula I include salts, prodrugs and solvates. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are
15 quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a
20 medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates,
25 ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates,
30 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates,

sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates, undecanoates, and the like.

Exemplary basic salts (formed, for example, where the R substituents comprise
5 an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the
10 like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

15

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the Formula I, or a salt and/or solvate thereof. Solvates
20 of the compounds of Formula I are preferably hydrates.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound of the formula I, including enantiomeric and diastereomeric forms, are contemplated within the scope of
25 this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

30

The compounds of Formula I are typically employed as part of a pharmaceutical composition including a pharmaceutically acceptable carrier for the treatment of respiratory and non-respiratory diseases. The compounds employed for this purpose are typically administered in an amount of from about 0.01 to 100 mg/kg/day.

- 5 The compounds of Formula I are especially effective in inhibiting the PDE7 enzyme. Additionally a subset of compounds are also effective at inhibiting PDE4.

The pharmaceutical composition comprising at least one compound of Formula I may be formulated, for example, by employing conventional solid or liquid vehicles or
10 diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

15 The compounds of Formula I may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as
20 in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may be based for immediate release or extended release by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as
25 subcutaneous implants or osmotic pumps. The present compounds may also be administered liposomally.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or
30 sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release

tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The present compounds may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

15

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

20

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

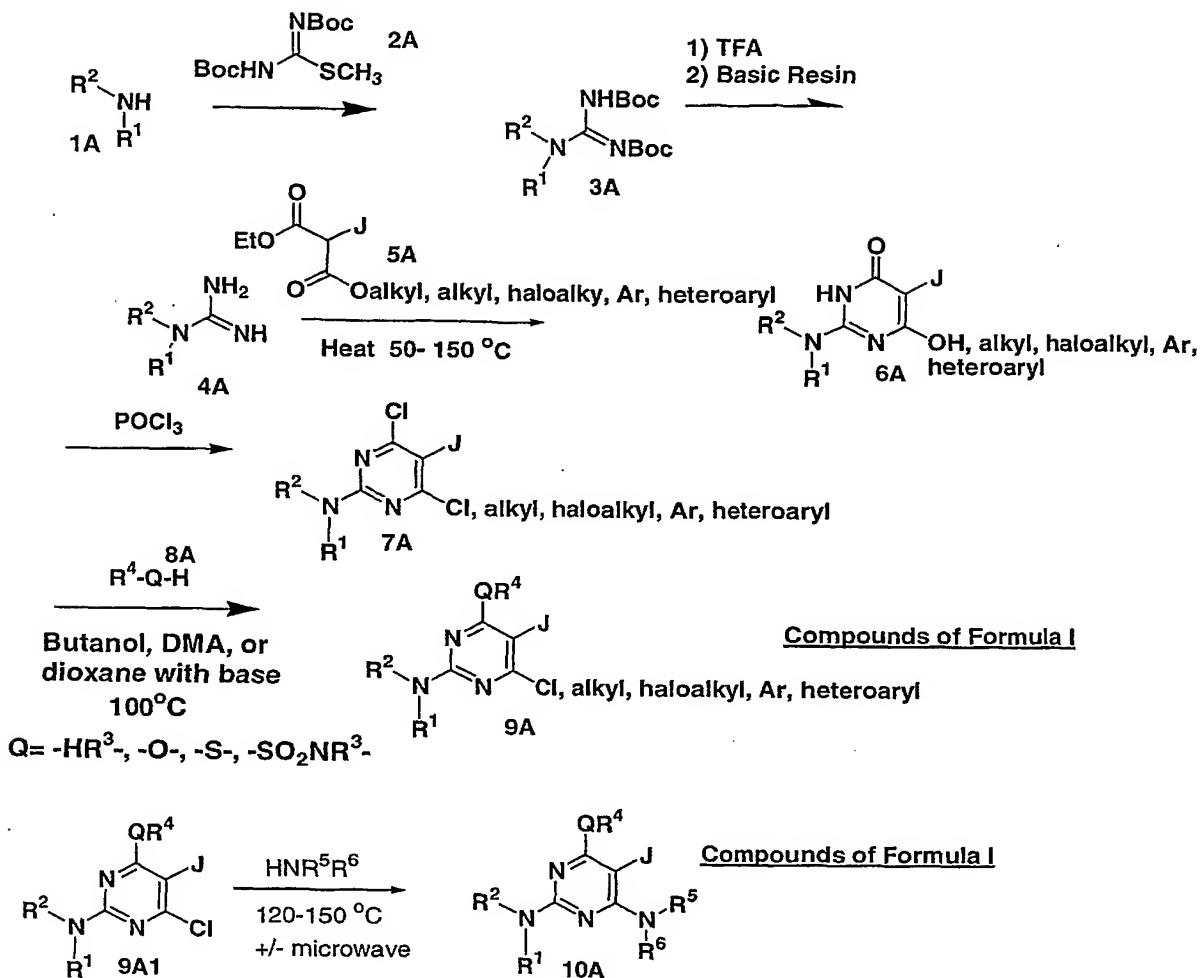
5 The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human from about 0.01 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level
10 and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects
15 for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to leukocyte activation or respiratory cell-associated disorders.

Methods of Preparation

20 Compounds of Formula I may be prepared by reference to the methods illustrated in the following Schemes A through B. As shown therein the end product is a compound having the same structural formula as Formula I. It will be understood that any compound of Formula I may be produced by Scheme A and B by the suitable
25 selection of appropriate substitution. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. All documents cited are incorporated herein by reference in their entirety. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Constituents of compounds are as defined herein or elsewhere in the specification.

Compounds of formula I may be prepared from readily available starting materials by a number of methods known to one skilled in the art of organic chemistry and is illustrated in Scheme A1. An amine **1A** is reacted with reagent **2A** to provide guanidine **3A** which is deprotected and freebased to yield guanidine **4A**. Reaction with either a beta-keto ester **5A** or a malonate **5A** with heat with or without added base condenses to produce pyrimidine **6A**. beta-Keto ester **5A** or malonate **5A** are either commercially available or readily prepared by methods well known in the literature. For examples see Advanced Organic Chemistry 3rd edition (1990, Plenum Press New York) Carey, F and Sundberg, R., chapter 2 section 2, and Comprehensive Organic Transformations, (1989 VCH publishers NY). This pyrimidine **6A** is reacted with phosphorous oxychloride to produce intermediate pyrimidine **7A**. Reaction with reagent **8A** which may be an amine or an alcohol, a thiol or a sulfonamide on the presence of a suitable base to provide pyrimidines **9A**, which are compounds of Formula I. In the case of pyrimidine **9A1**, the chloro group may be replaced by an amine by reaction at elevated temperature, or, in some cases with the aid of a microwave apparatus, to produce pyrimidine **10** which are also compounds of Formula I.

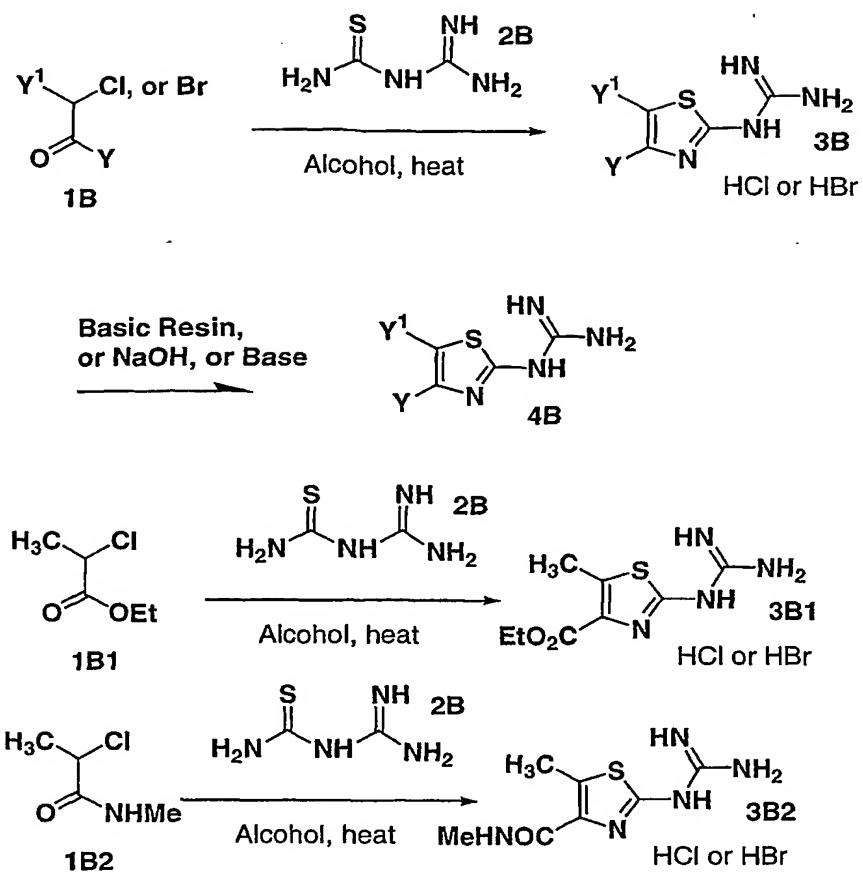
Scheme A1



In some instances the intermediate guanidines **4A** might be readily prepared by direct synthesis, an example of which is illustrated in scheme **B1**. *alpha*-Haloketone **1B** is reacted with a thiobiuret such as **2B** to provide the guanidine salt **3B**. Intermediates **3B1** and **3B2** are of particular utility to this invention. The guanidine salt, if required may be liberated to its free base by treatment with a basic resin, or sodium hydroxide, sodium methoxide, or an amine base to provide intermediate **4B**, which can be further elaborated to compounds of formula I as illustrated in scheme **A1**.

10

Scheme B1



5

Utility

Selective PDE7 inhibitors or dual PDE7-PDE4 inhibitors including compounds of formulas I, are useful in the treatment (including prevention, partial alleviation or cure) of leukocyte activation-associated disorders, which include (but are not limited to) disorders such as: transplant rejection (such as organ transplant, acute transplant, xenotransplant or heterograft or homograft such as is employed in burn treatment); protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; respiratory and pulmonary diseases including but not limited to asthma, exercise induced asthma, chronic obstructive pulmonary disease

(COPD), emphysema, bronchitis, and acute respiratory distress syndrome (ARDS); inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosis); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis; serum sickness; urticaria; allergic diseases such as respiratory allergies (e.g., asthma, hayfever, allergic rhinitis) or skin allergies; scleroderma; mycosis fungoides; acute inflammatory and respiratory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplantaris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic sclerosis; and morphea.

The term "leukocyte activation-associated disorder" or "leukocyte activation-mediated disorder" as used herein includes each of the above referenced diseases or disorders. The compounds of the present invention are useful for treating the aforementioned exemplary disorders irrespective of their etiology.

Those present compounds which are dual PDE7/4 inhibitors may be more effective than either a selective PDE4 inhibitor or a selective PDE7 inhibitor in the above mentioned disease states, as a result of either additive or synergistic activity resulting from the combined inhibition of PDE7 and PDE4.

The present invention thus provides methods for the treatment of disorders as discussed above comprising the step of administering to a subject in need thereof of at least one selective PDE7 inhibitor or at least one dual PDE7-PDE4 inhibitor for the

treatment of leukocyte activation-associated or leukocyte-activation mediated disease. Other therapeutic agents such as those described below may be employed with the compounds of the present invention. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

The methods of treating diseases which would benefit from the inhibition of PDE7 or the inhibition of both PDE7-PDE4 by a dual agent may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions such as: immunosuppressants such as, cyclosporins (e.g., cyclosporin A), anti-IL-1 agents, such as Anakinra, the IL-1 receptor antagonist, CTLA4-Ig, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3, anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and CD154, such as antibodies specific for CD40 and/or CD154 (i.e., CD40L), fusion proteins constructed from CD40 and CD154 (CD40Ig and CD8-CD154), interferon beta, interferon gamma, methotrexate, FK506 (tacrolimus, Prograf), rapamycin (sirolimus or Rapamune)mycophenolate mofetil, leflunomide (Arava), azathioprine and cyclophosphamide, inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), or derivatives thereof, steroids such as prednisone or dexamethasone, gold compounds TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel), inhibitors of p-38 kinase such as BIRB-796, RO-3201195, VX-850, and VX-750, β -agonists such as albuterol, levalbuterol (Xopenex), and salmeterol (Serevent), inhibitors of leukotriene synthesis such as montelukast (Singulair) and zariflukast (Accolate), and anticholinergic agents such as ipratropium bromide (Atrovent), PDE4 inhibitors such as Arofylline, Cilomilast, Roflumilast, C-11294A, CDC-801, BAY-19-8004, Cipamylline, SCH351591, YM-976, PD-189659, Mesipramine, Pumafentriptane, CDC-998, IC-485, and KW-4490, PDE7 inhibitors such as IC242, (*Lee, et. al. PDE7A is expressed in human B-lymphocytes and is*

up-regulated by elevation of intracellular cAMP. *Cell Signalling*, 14, 277-284, (2002)) and also include compounds disclosed in the following patent documents: WO 0068230, WO 0129049, WO 0132618, WO 0134601, WO 0136425, WO 0174786, WO 0198274, WO 0228847, U.S. Provisional Application Serial No. 60/287,964, and U.S. Provisional
5 Application Serial No. 60/355,141 anti-cytokines such as anti-IL-1 mAb or IL-1 receptor agonist, anti-IL-4 or IL-4 receptor fusion proteins and PTK inhibitors such as those disclosed in the following U.S. Patents and Applications, incorporated herein by reference in their entirety: U.S Patent No. 6,235,740, U.S. Patent No. 6,239,133, U.S.
10 Application Serial No. 60/065,042, filed 11/10/97 (Attorney Docket No. QA207*), U.S. Application Serial No. 09/173,413, filed 10/15/98 (Attorney Docket No. QA 207a), and U.S. Patent No. 5,990,109.

See the following documents and references cited therein: Hollenbaugh, D., Douthwright, J., McDonald, V., and Aruffo, A., "Cleavable CD40Ig fusion proteins and the binding to sgp39", *J. Immunol. Methods* (Netherlands), 188(1), p. 1-7 (Dec 15 1995);
15 Hollenbaugh, D., Grosmaire, L.S., Kullas, C.D., Chalupny, N.J., Braesch-Andersen, S., Noelle, R.J., Stamenkovic, I., Ledbetter, J.A., and Aruffo, A., "The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity", *EMBO J* (England), 11(12), p 4313-4321 (Dec 1992); and Moreland, L.W. et al., "Treatment of rheumatoid arthritis
20 with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein, *New England J. of Medicine*, 337(3), p. 141-147 (1997).

Compounds present invention (especially selective PDE 7 inhibitors) may also be employed in combination with PDE 4 inhibitors. Examples of selective PDE4 inhibitors currently in development, which can be used in combination with compounds
25 of the present invention include Arofylline, Cilomilast, Roflumilast, C-11294A, CDC-801, BAY-19-8004, Cipamylline, SCH351591, YM-976, PD-189659, Mesipram, Pumafentline, CDC-998, IC-485, and KW-4490.

The above other therapeutic agents, when employed in combination with the
30 compounds of the present invention, may be used, for example, in those amounts

indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Use of the compounds of the present invention as encompassed by formula I in
5 treating leukocyte activation-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: transplant (such as organ transplant, acute transplant, xenotransplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or
10 other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; respiratory and pulmonary diseases including but not limited to asthma, exercise induced asthma, chronic obstructive pulmonary disease (COPD), emphysema, bronchitis, and acute respiratory distress syndrome (ARDS); inflammatory bowel disease, including ulcerative colitis and Crohn's
15 disease; lupus (systemic lupus erythematosis); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease
20 (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis; serum sickness; uticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleracierma;
25 mycosis fungoides; acute inflammatory and respiratory responses (such as acute respiratory distress syndrome and ishchemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplantaris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic schlerosis; and morphea.
30 The combined activity of the present compounds towards T-cells and other PDE7-expressing cells may be of value in the treatment of any of the aforementioned

disorders. Additionally those present compounds which are dual PDE4/7 inhibitors may be more effective than either a selective PDE4 inhibitor or a selective PDE7 inhibitor in the above mentioned disease states.

In a particular embodiment, the compounds of the present invention are useful
5 for the treatment of the aforementioned exemplary disorders irrespective of their etiology,
for example, for the treatment of transplant rejection, rheumatoid arthritis, multiple
sclerosis, chronic obstructive pulmonary disease, inflammatory bowel disease, lupus,
graft v. host disease, T-cell mediated hypersensitivity disease, psoriasis, Hashimoto's
thyroiditis, Guillain-Barre syndrome, cancer, contact dermatitis, allergic disease such as
10 allergic rhinitis, asthma, ischemic or reperfusion injury, respiratory diseases such as
asthma, COPD and bronchitis or atopic dermatitis whether or not associated with
leukocyte activation.

15 *PDE-containing cell lysates*

Hut78 cells were grown in 10% FCS in Iscoves Modified Dulbecco's Medium (Gibco BRL-Life Technologies, Grand Island, NY) with antibiotics. Cells were centrifuged and resuspended in four volumes of [40 mM Tris (pH 7.5)/50 µM EDTA/200µM PMSF with a cocktail of Protease inhibitors (Boehringer Mannheim, 20 Indianapolis, IN)] at 4C. Cells were homogenized using a Virtis homogenizer, and the lysate was centrifuged twice for 15 min at 15,000 × g. Glycerol was added to a final volume of 50% for storage at -20C.

SPA assay

25 Inhibition of PDE activity in Hut78 cell lysate was determined using an SPA specific for cAMP (Amersham Pharmacia Biotech, Buckinghamshire, UK) according to the manufacturers instructions with minor modifications. Enzyme assays were performed at room temperature in the presence of 50mM Tris HCl, pH7.5, containing 8.3mM MgCl₂, 1.7mM EGTA and 0.5mg/mL BSA. Each assay was performed in a 100µL reaction volume in 96 well microtitre plates containing the above buffer, 0.3ul of Hut78 cell lysate treated with 2 uM Zardaverine to inhibit PDE3 and PDE4, 0.05 uCi of [³⁵S]-

³H] Adenosine 3',5'-cyclic phosphate as an ammonium salt for 20 min. The reaction was terminated by the addition of 50 μ l PDE SPA beads (1mg) water with 10mM cold cAMP (Sigma, St. Louis MO). The reaction mix was allowed to settle for 20 minutes before counting in a Top Count-NXT scintillation counter (Packard BioScience, Meriden, CT).

- 5 For individual PDE enzymes other than PDE7, the assay was essentially unchanged except that ³H-cyclic GMP was used as the substrate for PDE1, PDE5 and PDE6. The following PDEs/activators and enzyme sources were used: PDE1, bovine (Sigma St Louis), calmodulin; PDE2, rat kidney, cGMP; PDE3, human platelet; PDE4, rat kidney; PDE5, human platelet, and PDE6, bovine retina.

10

T cell Proliferation Assay

Peripheral blood mononuclear cells (PBMC) were isolated from whole blood by density gradient centrifugation over Lymphoprep, 1.077. Cells were plated into 96 well U-bottom plates at 2.5x10⁵ cells/well in 10% FBS RPMI 1640 (Life Technologies/Gibco-BRL) containing 10 μ g/ml anti-CD3 (G19-4, Bristol-Myers Squibb P.R.I., Princeton, NJ) and 1 μ g/ml anti-CD28 (9.3, Bristol-Myers Squibb P.R.I.) in the presence and absence of inhibitors. DMSO (used as a solvent for inhibitors) was added to the medium at 0.1% final concentration. The total volume per well was 200 μ L. Cells were incubated at 37C 5% CO₂ for 3 days, at which time 0.5 μ Ci of ³H-thymidine was added to each well. Six hours following the addition of ³H-thymidine, the plates were harvested onto filter plates, 30 μ l EcoLite scintillant (ICN, Costa Mesa, CA) was added per well, and plates read on a Top Count-NXT scintillation counter.

TNF α secretion assay

25 The ability of compounds to inhibit the production and secretion of TNF α from leukocytes was performed using either PBMC (obtained as described above) or the THP-1 cell line as a source of monocytes. Compounds were diluted in RPMI 1640 supplemented with 10% FBS and DMSO at a final concentration of 0.2%. Cells (2x10⁵/well in U-bottom 96 well plates) were pre-incubated with compounds for 30 min 30 at 37 C prior to addition of lipopolysaccharide (LPS) at a final concentration of 6.25 ng/ml in a total volume of 200 μ L. After 4h at 37C, 50 μ L of supernatant was carefully

aspirated for detection of soluble TNF α . Soluble TNF α was detected by ELISA developed by R&D Systems (Minneapolis, MN) according to the manufacturers instructions.

Examples

5

The following examples illustrate preferred embodiments of the present invention and do not limit the scope of the present invention which is defined in the claims.

Abbreviations employed in the Examples are defined below. Compounds of the Examples are identified by the example and step in which they are prepared (e.g., "A1.1" denotes the title compound of step 1 of Example A1), or by the example only where the compound is the title compound of the example (for example, "A2" denotes the title compound of Example A2).

Abbreviations

	Ac	Acetyl
15	AcOH	Acetic acid
	aq.	Aqueous
	CDI	Carbonyldiimidazole
	Bn	Benzyl
	Bu	Butyl
20	Boc or BOC	tert-butoxycarbonyl
	DMAP	Dimethylaminopyridine
	DMA	N,N-Dimethylacetamide
	DMF	dimethylformamide
	DMSO	Dimethylsulfoxide
25	EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	EtOAc	Ethyl acetate
	Et	Ethyl
	EtOH	Ethanol
	H	Hydrogen
30	h	Hours
	i	<i>iso</i>

	HPLC	High pressure liquid chromatography
	HOAc	Acetic acid
	Lawesson's Reagent	[2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2-4-disulfide
5	LC	liquid chromatography
	Me	Methyl
	MeOH	Methanol
	min.	Minutes
	M ⁺	(M+H) ⁺
10	M ⁺¹	(M+H) ⁺
	MS	Mass spectrometry
	n	<i>normal</i>
	ON	over night
	Pd/C	Palladium on carbon
15	Ph	Phenyl
	Pr	Propyl
	Ret Time	Retention time
	rt or RT	Room temperature
	sat.	Saturated
20	S-Tol-BINAP	(S)-(-)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl
	t	<i>tert</i>
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	YMC	YMC Inc, Wilmington, NC 28403

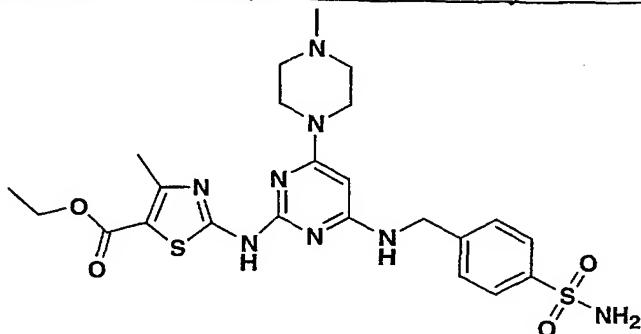
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HPLC conditions used to determine retention times; 2 min gradient 0-100% B in A(A; 0.1% TFA in 90/10 water/methanol; B; 0.1%TFA in 10/90 water/methanol) using a YMC turbopack column at with a detection wavelength of 220 nanometeres or 254 nanometers.

30

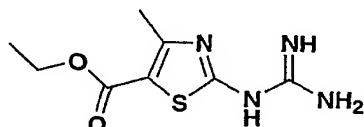
Example A1

2-[[4-[[(4-(Aminosulfonyl)phenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester



5

A1.1: 2-[(Aminoiminomethyl)amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester



10

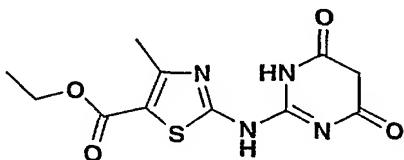
A1.1

A solution of 2-imino-4-thiobiuret (20.0g, 0.17 mol), 2-chloroacetoacetate (28g, 0.17 mol) in ethanol (500 mL) was heated to 100°C for 4 hours. The reaction mixture was concentrated to half volume and poured into 1 liter of 1N NaOH. The white solid which precipitated out was collected by filtration and dried under vacuum to yield **A1.1** (30.5g, 79%). $^1\text{H-NMR}$ (DMSO- d_6) δ : 4.22 (2H, q, $J = 7$ Hz), 2.50 (3H, merge with DMSO), 1.26 (3H, t, $J = 7$ Hz). HPLC: 97.7%, ret. time = 1.619 min., LC/MS ($M+\text{H}^+$) = 229.

15

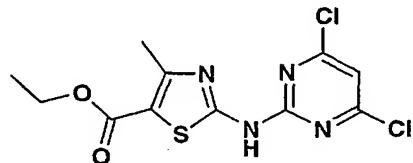
A1.2: 2-[(4-6(1H,5H)-pyrimidinedion-2-yl)amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

20

**A1.2**

To a solution of **A1.1** (5.7 g, 25 mmol) in ethanol (250 mL) was added 21% sodium ethoxide in ethanol (7.75mL, 25 mmol). The reaction mixture was heated in an oil bath at 100°C for 15 minutes during which time most, but not all, of the material had dissolved, and Diethylmalonate (3.8 g, 25 mmol) was added. The reaction mixture was maintained in an oil bath to 100°C for 2 hours. An additional 4mL of 21% sodium ethoxide in ethanol and additional 2 mL of diethylmalonate were added and the reaction mixture refluxed for an additional 2 hours after which HPLC analysis indicated only a trace amount of starting material remained. The reaction mixture was allowed to cool to room temperature and the copious crystals which precipitated out were collected by filtration and dried to yield **A1.2** solvated with 1 molecule of ethanol (7.6 g, 89% based on solvate). ¹H-NMR (DMSO-d₆) δ: 9.75 (1H, br s) 4.45 (1H, t, J = 4Hz), 4.14 (2H, q, J = 7 Hz), 3.45 (2H, m) 2.56 (3H, s), 1.29 (3H, t, J = 7 Hz). 1.05 (3H, t, J = 7 Hz), HPLC: 91.5%, ret. time = 2.836 min., LC/MS (M+H)⁺ = 297.

A1.3: 2-[[(4-6-Dichloropyrimidin-2-yl)amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

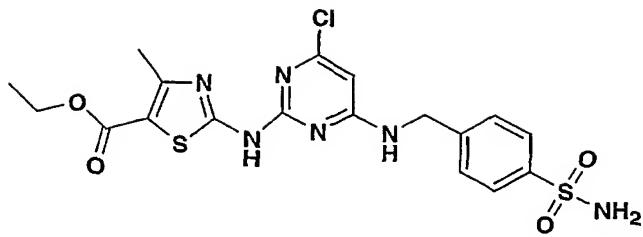


A1.3

A suspension of **A1.2** (7.6 g, 22 mmol) in POCl₃ (54 ml) was heated at 100°C for 16 hours and then it was cooled down to RT which was poured into 500g of ice. After the ice melted the solid was collected by filtration and triturated with hot methanol. The solid was then dried under vacuum to yield. **A1.3** (6.2 g, 84%). ¹H-NMR (DMSO-d₆) δ: 7.55 (1H, s), 4.27 (2H, q, J = 7 Hz), 2.56 (3H, s), 1.29 (3H, t, J = 7 Hz). HPLC: 97%, ret. time = 3.929 min., LC/MS (M+H)⁺ = 333.

25

A1.4: 2-[[(4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-chloro-2-pyrimidinyl]aminol-4-methyl-5-thiazolecarboxylic acid ethyl ester

**A1.4**

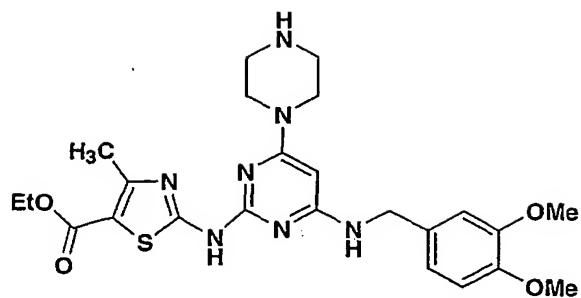
A suspension solution of **A1.3** (33 mg, 0.1 mmol), *p*-aminomethylbenzenesulfonamide•HCl (24 mg, 0.106 mmol) and diisopropylethylamine (58 mg, 0.45 mmol) in n-butanol (2 mL) was heated to 105°C for 2 hours and then it was cooled down to RT. The solid was precipitated out which was collected with filtration to yield **A1.4** (31.8 mg, 66 %). $^1\text{H-NMR}$ (DMSO-d₆) δ: 7.77 (2H, d, J = 8 Hz), 7.52 (2H, d, J = 8 Hz), 7.31 (2H, s), 6.27 (1H, s), 4.81 (2H, m), 4.22 (2H, q, J = 7 Hz), 2.50 (3H, merge with DMSO), 1.26 (3H, t, J = 7 Hz). HPLC: 96%, ret. time = 3.232 min., LC/MS (M+H)⁺ = 483.

A1.5: 2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

A solution of **A1.4** (21.8 mg, 0.045 mmol) and 1-methylpiperazine (90 mg, 0.9 mmol) in dimethylacetamide (0.5 ml) was heated to 120 to 130°C for half an hour. The reaction mixture was concentrated to yield a crude product which was added 1 mL of methanol and stirred for 20 minutes. The solid was precipitated out which was collected with filtration to yield **A1** (12.5 mg, 51 %). $^1\text{H-NMR}$ (DMSO-d₆) δ: 11.17 (1H, s), 7.75 (2H, d, J = 8 Hz), 7.50 (2H, d, J = 8 Hz), 7.28 (2H, s), 5.40 (1H, s), 4.65 (2H, m), 4.19 (2H, q, J = 7 Hz), 3.48 (4H, m), 3.17 (3H, d, J = 5 Hz), 2.50 (3H, merge with DMSO), 2.10-2.50 (4H, m), 1.26 (3H, t, J = 7 Hz). HPLC: 88.3%, ret. time = 1.979 min., LC/MS (M+H)⁺ = 547.

Example A2

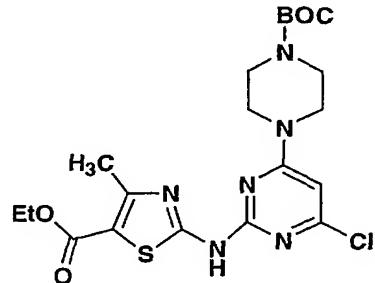
2-[[4-[(3,4-Dimethoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester trifluoroacetate salt



A2

A2.1: 2-[[4-chloro-6-(4-tertbutyloxycarbonyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

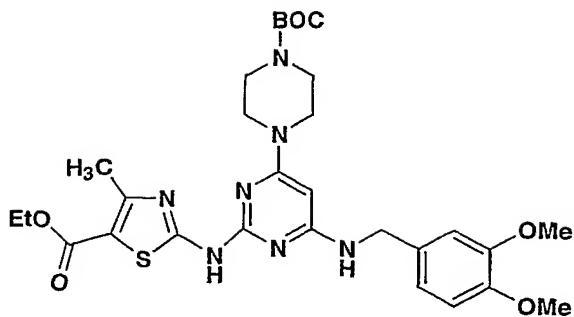
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A2.1

A suspension solution of **A1.3** (800mg, 2.4 mmol), 1-*tert*-butoxycarbonylpiperazine (470 mg, 2.5 mmol) and diisopropylethylamine (1.8 ml, 10.6 mmol) in *n*-butanol (16 mL) was heated to 105°C for 3 hours. After cooling to room temperature, the precipitated solid was collected by filtration and washed with methanol to yield **A2.1** (1.1 g, 94%). ¹H-NMR (DMSO-d₆) δ: 6.61 (1H, s), 4.22 (2H, q, J = 7 Hz), 3.75 (1H, br. s), 3.45 (4H, br. s), 3.30 (4H, br. s), 2.50 (3H, merge with DMSO), 1.43 (9H, s), 1.28 (3H, t, J = 7 Hz). HPLC: 95%, ret. time = 3.320 min., LC/MS (M+H)⁺ = 483.

A2.2: 2-[[4-[(3,4-Dimethoxyphenyl)methyl]amino]-6-(4-tertbutyloxycarbonyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester



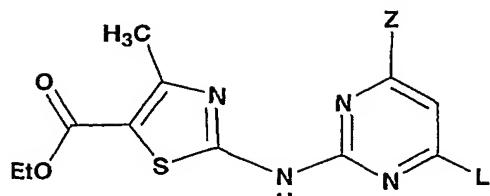
A solution of **A2.1** (40.0 mg, 0.08 mmol) and veratrylamine (30.0 mg, 0.18 mmol) in n-butanol (0.5 ml) was heated to 130°C overnight. After cooling to room temperature, the precipitated solid was collected by filtration and washed with methanol to yield **A2.2** (37.2 mg, 73 %). ¹H-NMR (DMSO-d₆) δ: 6.99 (1H, s), 6.88 (2H, s), 5.39 (1H, s), 4.48 (1H, br. s), 4.18 (2H, q, J = 7 Hz), 3.72 (3H, s), 3.71 (3H, s), 3.51 (4H, br. s), 3.40 (4H, br. s), 2.50 (3H, merge with DMSO), 1.42 (9H, s), 1.24 (3H, t, J = 7 Hz). HPLC: 95%, ret. time = 3.080 min., LC/MS (M+H)⁺ = 614.

10

A2.3: 2-[[4-[(3,4-Dimethoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyloxy]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester trifluoroacetate salt

Trifluoroacetic acid (10% solution in dichloromethane, 0.6 ml) was added in one portion to a stirred solution of compound **A2.2** (21.3 mg, 0.035 mmol). After stirring for 2 hours at room temperature, diethyl ether was added (2 ml) and the solution was concentrated *in vacuo*. Two subsequent additions of diethyl ether (2 x 2 ml) followed by concentration *in vacuo* left the trifluoroacetic acid salt of compound **A2**. HPLC: 95%, ret. time = 2.020 min., LC/MS (M+H)⁺ = 514.

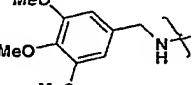
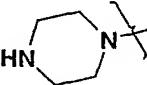
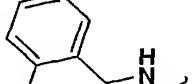
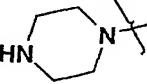
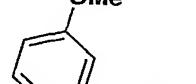
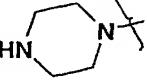
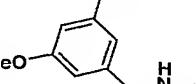
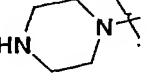
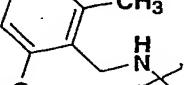
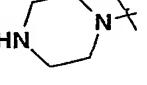
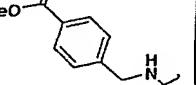
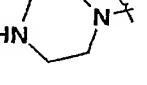
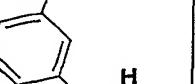
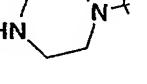
Example A3-A214

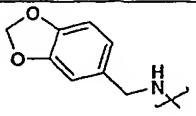
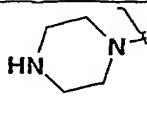
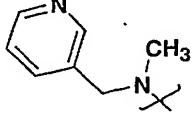
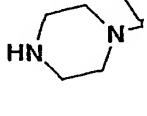
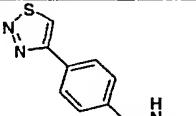
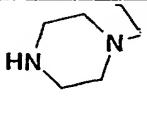
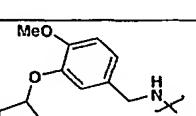
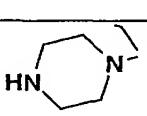
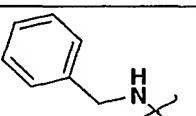
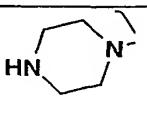
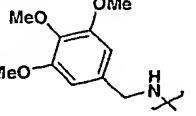
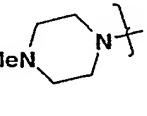
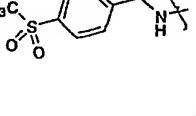
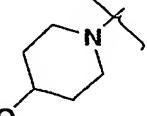


Examples A3 to A214 were prepared in a similar manner to that used for Example A1 or A2 utilizing the appropriate amines. Examples A61 and A62 used only a single amine addition step as in A2.1, substituting the appropriate amine. Example A63 was prepared in a manner similar to step A1.5 except that sodium ethoxide was used in place of an amine.

Table A

Ex.	L	Z	Name	HPLC Retention ^a (min)	MS Reported
A3			2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.98	533.18
A4			4-Methyl-2-[[4-[[[4-(methylsulfonyl)phenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.05	532.36
A5			2-[[4-[[4-Methoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	2.15	484.56
A6			2-[[4-[[[(3-Methoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.50	484.16
A7			2-[[4-[[[(2-Methoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-	1.51	484.16

			5-thiazolecarboxylic acid ethyl ester		
A8			4-Methyl-2-[[4-(1-piperazinyl)-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.44	544.19
A9			2-[[4-[(2-Ethoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	2.29	498.64
A10			2-[[4-[(2,5-Dimethoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	2.22	514.59
A11			2-[[4-[(3,5-Dimethoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.54	514.18
A12			2-[[4-[(2,6-Dimethylphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.65	482.15
A13			2-[[4-[(4-(Methoxycarbonyl)phenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.53	512.17
A14			2-[[4-[(3-Bromophenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.68	532.04

A15			2-[[4-[(1,3-Benzodioxol-5-ylmethyl)amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	2.13	498.48
A16			4-Methyl-2-[(4-methyl(3-pyridinyl)methyl)amino]-6-(1-piperazinyl)-2-pyrimidinylamino]-5-thiazolecarboxylic acid ethyl ester	1.71	469.55
A17			4-Methyl-2-[(4-(1-piperazinyl)-6-[[[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	2.18	538.42
A18			2-[[4-[[3-(Cyclopentyloxy)-4-methoxyphenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	2.46	568.56
A19			4-Methyl-2-[(4-[(phenylmethyl)amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	2.13	454.53
A20			4-Methyl-2-[(4-(4-methyl-1-piperazinyl)-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.19	558.49
A21			2-[[4-(4-Hydroxy-1-piperidinyl)-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.27	547.20

A22			4-Methyl-2-[[4-[[2-(1-methylethoxy)ethyl]amino]-6-[(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinylamino]-5-thiazolecarboxylic acid ethyl ester	1.13	574.39
A23			2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.26	574.33
A24			2-[[4-[[2-(1 <i>H</i> -imidazol-4-yl)ethyl]amino]-6-[(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.13	557.32
A25			4-Methyl-2-[[4-[[4-(methylsulfonyl)phenyl]methyl]amino]-6-[[3-(4-morpholinyl)propyl]amino]-2-pyrimidinylamino]-5-thiazolecarboxylic acid ethyl ester	1.13	590.37
A26			2-[[4-[(2-Methoxy-1-methylethyl)amino]-6-[(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.34	535.35
A27			4-Methyl-2-[[4-[[4-(methylsulfonyl)phenyl]methyl]amino]-6-[[tetrahydro-2-furanyl]methyl]amino]-2-pyrimidinylamino]-5-thiazolecarboxylic acid ethyl ester	1.35	547.36

A28			2-[[4-[4-(2-Hydroxyethyl)-1-piperazinyl]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.60 ^a	575.21
A29			2-[[4-[2-(Aminocarbonyl)-1-pyrrolidinyl]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.41 ^a	560.14
A30			4-Methyl-2-[[4-[methyl(3-pyridylmethyl)amino]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.28 ^a	568.14
A31			2-[[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.33	561.35
A32			2-[[4-[2-(Diethylamino)ethyl]methylamino]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.33	576.17
A33			4-Methyl-2-[[4-[[[4-(methylsulfonyl)phenyl]methy]amino]-6-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.51	588.12

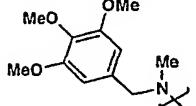
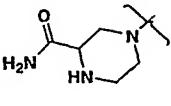
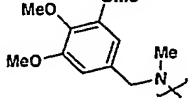
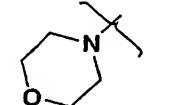
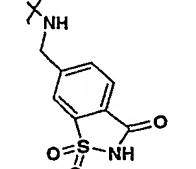
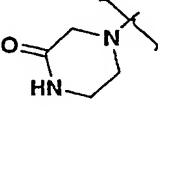
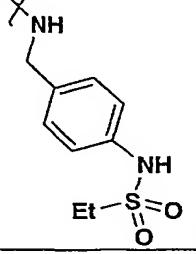
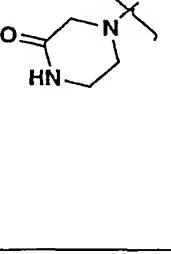
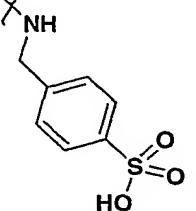
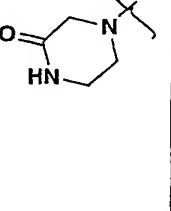
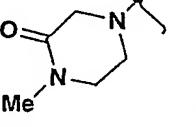
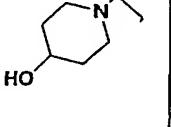
A34			2-[[4-[3-(Hydroxymethyl)-1-piperidinyl]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.58 ^a	561.18
A35			4-Methyl-2-[[4-(4-methyl-1-piperazinyl)-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.28 ^a	546.18
A36			2-[[4-[[2-[(Acetylamino)ethyl]amino]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.27 ^a	548.16
A37			2-[[4-(4-Ethyl-1-piperazinyl)-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.26 ^a	559.73
A38			2-[[4-(4-Acetyl-1-piperazinyl)-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.45 ^a	573.69
A39			2-[[4-[[2-(Dimethylamino)ethyl]amino]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.21	534.11

A40			2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.07 ^a	575.42
A41			2-[[4-(3-Hydroxy-1-pyrrolidinyl)-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.07 ^a	574.15
A42			2-[[4-[(4-Hydroxybutyl)amino]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.46	463.13
A43			2-[[4-[(2,3-Dihydroxypropyl)amino]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.35	537.12
A44			2-[[4-(4-Amino-1-piperidinyl)-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.25	546.12
A45			2-[[4-[4-Hydroxy-3-(hydroxymethyl)-1-piperidinyl]-6-[[[4-(methylsulfonyl)phenyl]methy]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.24	577.46

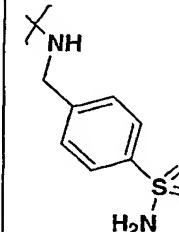
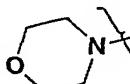
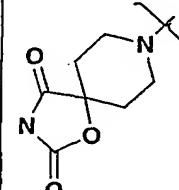
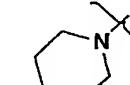
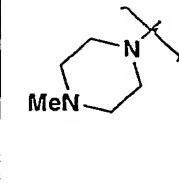
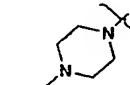
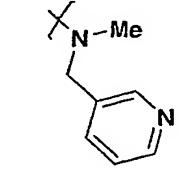
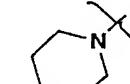
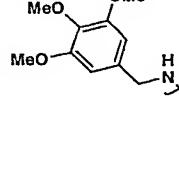
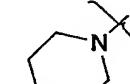
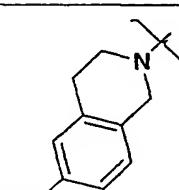
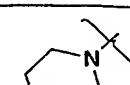
A46			2-[[4-(4-Dimethylamino-1-piperidinyl)-6-[[(4-methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.31	574.30
A47		-NHMe	2-[[4-[[(4-Aminosulfonyl)phenyl]methyl]amino]-6-(methylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.42	478.42
A48			2-[4,6-Bis-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.11	461.20
A49			2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.20	462.25
A50			2-[4-(3-Hydroxymethyl-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.33	476.20
A51			4-Methyl-2-[4-(4-methyl-piperazin-1-yl)-6-morpholin-4-yl-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester	1.30	448.22
A52			2-[4-(4-Amino-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	0.94	461.36
A53			2-[4,6-Bis-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.43 ^b	463.35

A54			2-[4-(4-oxo-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.11 ^c	461.38
A55			2-[4-(4-methyl-4-hydroxypiperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.31 ^c	476.31
A56			2-[4-(4-hydroxypiperidin-1-yl)-6-(4-dimethylmethyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.23 ^c	490.39
A57			2-[4-(4-hydroxymethyl-piperidin-1-yl)-6-(4-dimethylmethyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.27 ^c	504.41
A58			2-[4-(3-hydroxymethyl-piperidin-1-yl)-6-(4-dimethylmethyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.31 ^c	504.32
A59			2-[4-(4-hydroxymethyl-piperidin-1-yl)-6-(4-hydroxypiperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.52 ^c	476.93
A60			4-Methyl-2-[4-(4-hydroxypiperazin-1-yl)-6-morpholin-4-yl-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester	1.51 ^c	448.92
A61		-Cl	2-[[4-[[[4-(Methylsulfonyl)phenyl]methoxy]amino]-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.43 ^b	482.21

A62		-Cl	2-[[4-[[[4-(Aminosulfonyl)phenyl]methy l]amino]-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	3.23	483.11
A63			2-[[4-[4-(Dimethylamino)-1-piperidinyl]-6-[[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.38 ^b	586.21
A64			2-[[4-[1-piperizinyl]-6-methyl-6-[[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.48 ^c	558.30
A65			2-[[4-(4-Amino-1-piperidinyl)-6-[[[4-(methylsulfonyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester.	1.25	546.12
A66			2-[[4-[4-hydroxy-1-piperidinyl]-6-methyl-6-[[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.55	600.54
A67			2-[[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-methyl-6-[[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.52	587.32
A68			2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-oxo-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.36 ^c	462.19

A69			2-[[4-[3-(Aminocarbonyl)-1-piperizinyl]-6-methyl-6-((3,4,5-trimethoxyphenyl)methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.55 ^c	601.34
A70			2-[[4-[1-morpholinyl]-6-methyl-6-((3,4,5-trimethoxyphenyl)methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.67 ^c	559.32
A71			2-[[4-[3-Oxo-1-piperizinyl]-6-((1,1-dioxido-3-oxo-1,2-benzisothiazol-2-(3H)-yl)methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.29	573.08
A72			2-[[4-[3-Oxo-1-piperizinyl]-6-((4-(ethylsulfonylamino)phenyl)methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.43	574.69
A73			2-[[4-[3-Oxo-1-piperizinyl]-6-((4-hydroxysulfonylphenyl)methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.29 ^c	548.42
A74			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-methyl-3-oxo-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.43 ^c	476.53

A75			2-[4-(4-Dimethylamino)piperizin-1-yl]-6-(4-((1-pyrrolidinyl)carbonylmethyl)piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.17 ^c	586.35
A76			2-[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.36 ^b	587.17
A77			2-[4-(4-Amino-1-piperidinyl)-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.38 ^b	558.21
A78			2-[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-[4-[tetrazol-5-yl]-4-hydroxypiperidin-1-yl]2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.62	544.98
A79			2-[4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.55 ^c	572.35
A80			2-[4-[4-Hydroxy-1-piperidinyl]-6-[(4-hydroxysulfonyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.39 ^c	549.43
A81			2-[4-[(4-Cyanophenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate	1.36	479.14

			(1:1)		
A82			2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-(4-morpholinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester.	2.67	534.17
A83			2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(1-oxa-3,8-diazaspiro[4.5]decan-2,4,dion-8-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.49	532.52
A84			2-[4-(2-(Dimethylamino)ethyl)-piperazin-1-yl]-6-(4-methylpiperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.12 ^c	518.43
A85			2-[[4-(4-Hydroxy-1-piperidinyl)-6-[methyl(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.31 ^c	484.37
A86			2-[[4-[4-Hydroxy-3-hydroxymethylpiperidin-1-yl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.54	589.23
A87			2-[[4-(3,4-Dihydro-6,7-dihydroxy-2(1H)-isoquinolinyl)-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1)	1.45	526.19

A88			2-[[4-[4-((Methoxyacetyl)amino)-1-piperidinyl]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.45 ^b	618.16
A89			2-[[4-[[[3,4-Dimethoxyphenyl]methyl]amino]-6-[4-(dimethylamino)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.36 ^b	556.19
A90			2-[[4-[4-(Hydroxyethyl)piperidin-1-yl]-6-[4-(dimethylamino)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.10 ^c	519.34
A91			2-[[4-[4-(Dimethylamino)-1-piperidinyl]-6-[methyl(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.10 ^b	511.15
A92			2-[[4-[4-(Hydroxy)piperidin-1-yl]-6-[4-(methoxycarbonyl)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.57 ^c	505.22
A93			2-[[4-[4-(Hydroxy)piperidin-1-yl]-6-[4-(methyl)-4-(hydroxy)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.56 ^c	477.54
A94			2-[4-(3-oxopiperazin-1-yl)-6-(4-methylpiperazin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.23 ^c	461.26

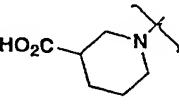
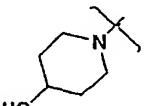
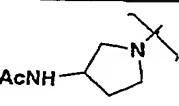
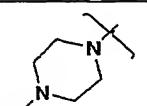
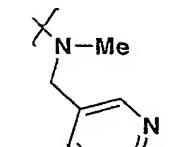
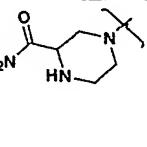
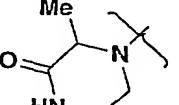
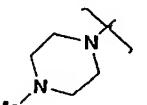
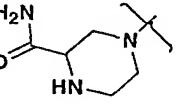
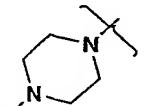
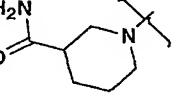
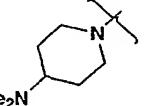
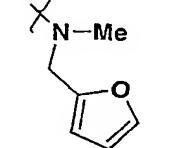
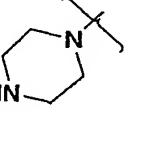
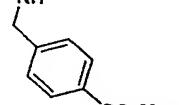
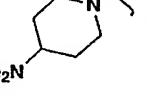
A95			2-[[4-[(4-Cyanophenyl)methyl]amino]-6-[4-(dimethylamino)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.47	493.10
A96			4-Methyl-2-[[4-[(3-nitrophenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1)	2.15	499.55
A97			2-[[4-(4-Hydroxy-1-piperidinyl)-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.59	559.18
A98			2-[4-(Dimethylamino)-piperazin-1-yl]-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.11 ^c	489.17
A99			2-[4-(Dimethylamino)-piperidin-1-yl]-6-(3-(aminocarbonyl)-1-piperazinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.17 ^c	518.65
A100			2-[4-(2-Hydroxyethyl)-piperazin-1-yl]-6-(4-methyl-1-piperazinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.10 ^c	491.38
A101			2-[[4-[(4-Aminocarbonyl)-1-piperidinyl]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.36 ^b	574.17

A102			2-[[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-[N-methyl-N-(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.34 ^c	498.39
A103			2-[[4-[4-Methylpiperazin-1-yl]-6-[(3,4-dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.34	528.15
A104			2-[[4-[piperazin-1-yl]-6-[(4-carboxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.30 ^b	512.19
A105			2-[[4-[3-Hydroxymethylpiperidin-1-yl]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.62 ^c	587.37
A106			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-carboxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.52 ^c	491.20
A107			2-[[4-[Piperazin-1-yl]-6-[(3,4-dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.90	514.55
A108			2-[[4-(4-Formyl-1-piperazinyl)-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.40 ^b	560.13

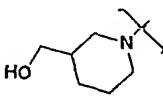
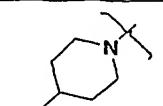
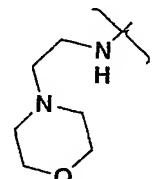
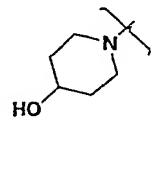
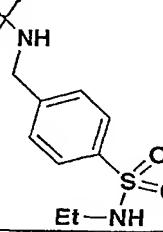
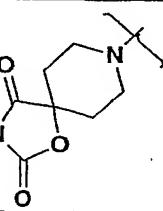
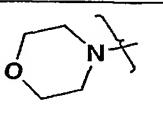
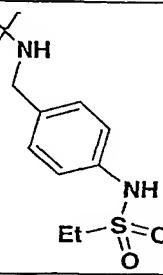
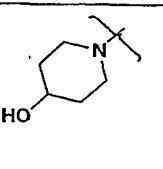
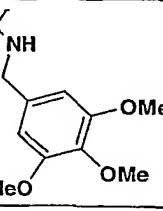
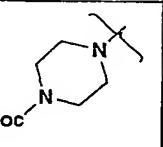
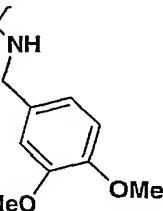
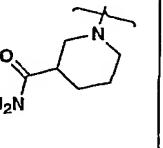
A109			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-(hydroxy)-4-(4-chlorophenyl)piperidin-1-yl)pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.83 ^c	573.20
A110			4-Methyl-2-[4-[4-dimethylamino-1-piperidinyl]-6-[(tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.29 ^c	490.39
A111			2-[[4-[Piperazin-1-yl]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.32	459.54
A112			2-[[4-[4-Morpholinyl]-6-[4-hydroxypiperidin-1-yl]2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.23	516.97
A113			2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2-(3H)-yl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.41	574.10
A114			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-(1-methyl-1-hydroxyethyl)piperidin-1-yl)pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.64 ^c	505.51
A115			2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[[N-methyl-N-(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.21 ^b	511.16

A116			2-[[4-[4-Hydroxymethyl-1-piperidinyl]-6-[[[(4-ethylsulfonylamino)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.58	589.74
A117			2-[[4-[4-Hydroxy-1-piperidinyl]-6-[4-[tetrazol-5-yl]-4-hydroxypiperidin-1-yl]2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.20	531.32
A118			2-[[4-[4-tertButyloxycarbonylamino-1-piperidinyl]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.76 ^c	672.70
A119			2-[[4-[(4-Cyanophenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1)	1.40	397.12
A120			2-[[4-[(2-Ethoxy-2-oxoethyl)amino]carbonyl]-1-piperazinyl]-6-[methyl(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1)	1.36	598.28
A121			2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.48 ^c	463.21

A122			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-hydroxy-4-phenyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.76 ^c	539.20
A123			4-Methyl-2-[4-[4-morpholinyl]-6-[(tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester	1.38 ^c	476.58
A124			2-[[4-[(Tetrahydro-2-furanyl)methyl]amino]-6-[[N-((3,4,5-trimethoxyphenyl)methyl)]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.30 ^c	573.31
A125			2-[[4-[4-Morpholinyl]-6-[(4-hydroxysulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.44 ^c	535.40
A126			2-[Bis-4,6-(4-Cyano-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	2.86	480.91
A127			2-[[4-[4-(Cyclopentylaminocarbonyl)-1-piperazinyl]-6-[N-methyl-N-(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.55	580.25
A128			2-[4-(2-Methoxyethyl)-piperazin-1-yl]-6-(4-methyl-1-piperazinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.15 ^c	505.39

A129			2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-carboxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.55 ^c	491.14
A130			2-[[4-[4-Methylpiperazin-1-yl]-6-[3-(acetylamino)-1-pyrrolidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.14 ^c	489.31
A131			2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[[N-methyl-N-(3-pyridinylmethyl)]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.13 ^b	512.13
A132			2-[[4-[2-Methyl-3-oxo-1-piperazinyl]-6-[4-methyl-1-piperazinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.32 ^c	475.36
A133			2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.09 ^b	490.16
A134			2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-(4-dimethylamino-1-piperidinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.21 ^c	517.39
A135			2-[[4-[1-piperazinyl]-6-[[N-methyl-N-(2-furylmethyl)]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.51	458.13
A136			2-[[4-[(4-Methoxycarbonylphenyl)methyl]amino]-6-(4-dimethyl-1-piperidinyl)-2-pyrimidinyl]amino]-4-methyl-	1.42 ^b	554.20

			5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1)		
A137			2-[4-[3-Oxo-1-piperazinyl]-6-[(4-(methylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.30	560.66
A138			2-[4-[3-Oxo-1-piperazinyl]-6-[(4-(propylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.49	588.71
A139			2-[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.54 ^b	586.20
A140			2-[Bis-4,6-(4-Hydroxy-4-methyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.65 ^c	491.53
A141			4-Methyl-2-[4-[4-dimethylamino-1-piperidinyl]-6-[(2-oxo-1-pyrrolidinyl)propyl]amino]-2-pyrimidinylamino]-5-thiazolecarboxylic acid ethyl ester	1.32 ^c	531.58
A142			2-[4-[3-Oxo-1-piperazinyl]-6-[(4-(iso-propylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.47	588.71

A143			2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-hydroxymethyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.54 ^c	477.19
A144			4-Methyl-2-[[4-[4-hydroxy-1-piperidinyl]-6-[(2-(4-morpholinyl)ethyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl	1.08 ^c	491.37
A145		-OMe	2-[[4-[[[4-(Ethylaminosulfonyl)phenyl]methoxy-6-amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, methyl ester, trifluoroacetate (1:1)	3.81	506.81
A146			2-[[4-[4-Morpholinyl]-6-[(1-oxa-3,8-diazaspiro[4.5]decan-2,4-dion-8-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.58	518.46
A147			2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(4-((ethylsulfonyl)amino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.51	575.71
A148			2-[[4-[tertButyloxycarbonyl-1-piperazinyl]-6-[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	4.00 ^d	644.65
A149			2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[[3,4-dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.54 ^b	556.14

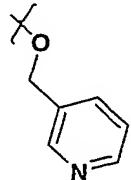
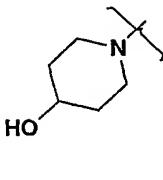
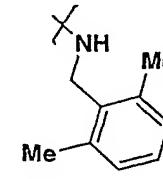
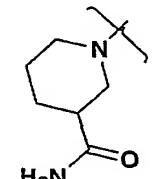
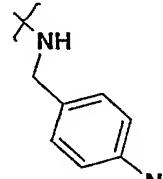
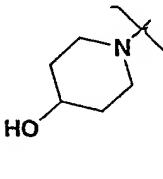
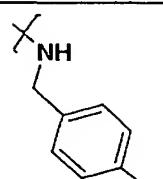
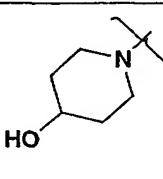
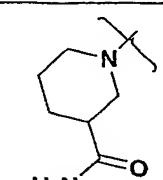
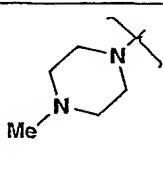
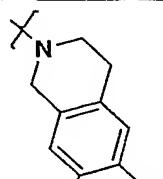
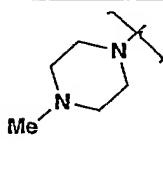
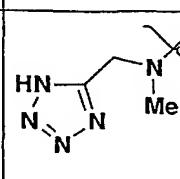
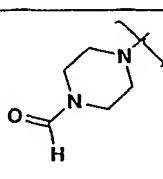
A150			2-[[4-[4-ethoxycarbonyl-1-piperazinyl]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester]	1.61	531.60
A151			2-[[4-[3-Oxo1-piperizinyl]-6-[(4-(cyclopropylsulfonylamino)phenyl)methyl]amino]2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.44	586.70
A152			2-[[4-[4-Hydroxymethyl-1-piperidinyl]-6-[(4-(methylsulfonylamino)phenyl)methyl]amino]2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.51	575.71
A153			2-[4-(4-Dimethylamino-1-piperazinyl)-6-(4-tertbutyloxycarbonylamino-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.55 ^c	589.44
A154			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-methoxymethyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.58 ^c	477.19
A155			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-hydroxyethyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.58 ^c	491.00
A156			2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-(hydroxy)-4-(3-trifluoromethylphenyl)piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.85 ^c	607.25

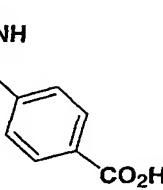
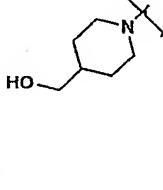
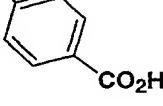
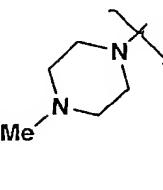
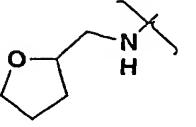
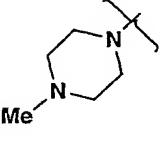
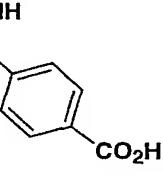
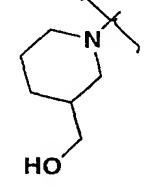
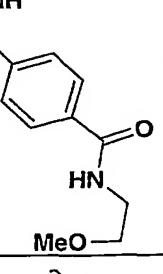
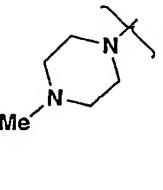
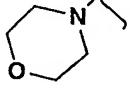
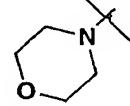
A157			2-[[4-[4-morpholinyl]-6-[4-[1-methyl-1-hydroxyethyl]-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.57 ^a	491.22
A158			2-[[4-[3-Oxo-1-piperizinyl]-6-[[3-pyridyl]oxy]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.35 ^c	456.19
A159			2-[[4-[4-Methyl-1-piperazinyl]-6-[(1,4-dioxaspiro[4.5]decan-8-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.43 ^b	504.25
A160			2-[[4-[4-Morpholinyl]-6-[(4-(methylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.53	547.66
A161			2-[[4-[3-Oxo-1-piperazinyl]-6-[(1-oxa-3,8-diazaspiro[4.5]decan-2,4-dion-8-yl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.46	531.47
A162			2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(4-(carboxyphenyl)methylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.37	513.31
A163			2-[[4-(4-Hydroxypiperidin-1-yl)-6-(4-(hydroxy)-4-(4-bromophenyl)piperidin-1-yl)-2-pyrimidinyl]amino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.76 ^a	619.42

A164			2-[4-[4-Morpholinyl]-6-[[[(4-(ethylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.55	561.69
A165			2-[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[[[(3,4-dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.35	557.14
A166			2-[4-[4-Formyl-1-piperazinyl]-6-[[[(3-(5-tetrazolyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.47	549.62
A167			2-[4-[4-(Hydroxymethyl)-1-Piperidinyl]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.35	489.23
A168			2-[4-[4-Methyl-1-piperazinyl]-6-[[[(2,5-dimethyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.58 ^b	496.17
A169	H		2-[2-[[[4-(Aminosulfonyl)phenyl)methyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.56	449.08
A170	H		2-[2-[[[4-(Methylsulfonyl)phenyl)methyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.82	448.02

A171			2-[[4-[3-(2-oxo-1-pyrrolidinyl)propyl]amino]-6-[N-methyl-N-(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.60 ^c	614.38
A172			2-[[4-[(1-Morpholinyl)]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.59	460.52
A173			2-[[4-[4-methyl-1-piperazinyl]-6-[4-[methylsulfonylamino]-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.25 ^b	539.41
A174			2-[[4-[4-hydroxy-1-piperidinyl]-6-[(2,5-dimethylphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.80 ^b	497.13
A175			4-Methyl-2-[[4-(4-morpholinyl)-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester	1.43 ^b	545.50
A176			2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-hydroxy-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.42 ^c	449.21
A177			4-Methyl-2-[[4-(4-methyl-1-piperazinyl)-6-[methyl(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester	1.12 ^b	483.18

A178			2-[[4-[3-Oxo-1-piperazinyl]-6-[[2-(5-(1H)tetrazolyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.52	535.59
A179			2-[[4-[2-Furylmethyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1)	1.32	444.15
A180			2-[[4-[(3,4-Dimethoxyphenyl)methyl]amino]-6-(4-morpholinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.65 ^b	515.13
A181			4-Methyl-2-[[4-[methyl(3-pyridinylmethyl)amino]-6-[(tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester	1.36 ^c	484.37
A182			2-[[4-[(4-hydroxy-1-piperidinyl)-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.30	475.20
A183			2-[4-(4-Hydroxypiperidin-1-yl)-6-[(4-hydroxy-4-(phenylmethyl)piperidin-1-yl)]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.66 ^a	553.35
A184			2-[4-(4-Dimethylamino-1-piperazinyl)-6-[[2-(1-morpholinyl)ethyl]amino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.04 ^c	519.35

A185			2-[[4-[4-hydroxy-1-piperidinyl]-6-[(3-pyridinylmethyl)oxy]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.50 ^c	471.05
A186			2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[(2,6-dimethylphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.74 ^b	524.14
A187			2-[[4-[4-hydroxy-1-piperidinyl]-6-[(4-(methylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.49	561.69
A188			2-[[4-[4-hydroxy-1-piperidinyl]-6-[(4-(propylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.60	589.74
A189			2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.10 ^b	489.43
A190			2-[[4-(3,4-Dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.53	554.42
A191			2-[[4-Formyl-1-piperazinyl]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid,	1.34	487.55

			ethyl ester		
A192			2-[[4-[(4-Carboxyphenyl)methyl]amino]-6-[4-(hydroxymethyl)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.57 ^b	527.16
A193			2-[[4-[(4-Carboxyphenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, monohydrochloride	1.30 ^b	512.19
A194			4-Methyl-2-[[4-(4-methyl-1-piperazinyl)-6-[(tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester	1.28 ^b	462.18
A195			2-[[4-[(4-Carboxyphenyl)methyl]amino]-6-[3-(hydroxymethyl)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.61 ^b	527.13
A196			2-[[4-[[4-[(2-Methoxyethyl)amino]carbonyl]phenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1)	1.27	569.26
A197			2-[4,6-Bis-(1-morpholinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.35 ^b	435.31

A198			2-[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.28	502.22
A199			4-Methyl-2-[4-[methyl(3-pyridinylmethyl)amino]-6-[4-morpholinyl]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester	1.35 ^b	470.12
A200			2-[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[[[4-(methoxycarbonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.47 ^b	555.15
A201		-Cl	2-[4-[4-hydroxy-1-piperidinyl]-6-chloro-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.50 ^c	398.18
A202		-Cl	2-[4-Chloro-6-[(1-oxa-3,8-diazaspiro[4.5]decan-2,4,dion-8-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.80	467.41
A203			2-[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.63	573.21
A204			2-[4-[3-(Hydroxymethyl)-1-piperidinyl]-6-[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.40	489.23
A205			2-[4-[3-(Hydroxymethyl)-1-pyrrolidinyl]-6-[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.42	474.55

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19097

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/55, 31/505; C07D 239/42, 403/04.
US CL : 514/211, 213, 230.5, 272, 273, 275; 544/51, 52, 320, 321, 323, 324, 330, 331, 332.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/211, 213, 230.5, 272, 273, 275; 544/51, 52, 320, 321, 323, 324, 330, 331, 332.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ON-LINE, EAST (IS & R)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,876,252 A (TORLEY et al) 24 October 1989 (24.10.1989), e.g., see compounds in Table IX on column 44.	1-5, and 9 -----
---		6-8, and 10-21
Y		
X	US 5,863,924 A (BERGER et al) 26 January 1999 (26.01.1999), column 42, compounds on lines 44-54.	1, 2, and 9 -----
---		3-8, and 10-21
Y		
X	WO 98/18782 A1 (CELLTECH THERAPEUTICS LIMITED) 07 May 1998 (07.05.1998), e.g., pages 24-26.	1-3, and 9 -----
---		4-8, and 10-21
Y		
X	PAUL, R. et. al. Preparation of Substituted N-Phenyl-4-aryl-2-pyrimidinamines as Mediator Release Inhibitors. J. Med. Chem., 1993, Vol. 36, No. 19, pages 2716-2725, especially page 2719. Table I, compounds 1-27, 1-28, 1-29.	1-5, and 9 -----
---		6-8, and 10-21
Y		

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"T"	
"B" earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

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WO 02/102313 A3

(54) Title: PYRIMIDINE INHIBITORS OF PHOSPHODIESTERASE (PDE) 7

(57) Abstract: Pyrimidine phosphodiesterase 7 (PDE 7) inhibitors of the following formula [insert chemical structure here] wherein R₁, R₂, Z, J and L are described herein, and analogs thereof are provided which are useful in treating T-cell mediated diseases.

17. A method of claim 10 wherein said T-cell mediated disorder is inflammatory bowel disease.

5 18. A method of claim 10 wherein said T-cell mediated disorder is ischemic or reperfusion injury.

19. A method of claim 10 wherein said T-cell mediated disorder is cell proliferation.

10 20. A method of claim 10 wherein the T-cell mediated disorder is psoriasis.

21. A pharmaceutical composition of claim 9 further comprising at least additional therapeutic agent selected from PDE 4 inhibitors, NSAIDs, COX-2 inhibitors, TNF- α inhibitors, beta-2 agonists, anti-cholinergic agents, and steroids.

15

c) optionally substituted (benzodioxole)alkyl;
R^{6a} is hydrogen;
or R^{5a} and R^{6a} together with the nitrogen atom to which they are attached may combine to
form a piperazine, piperadine or morpholine ring optionally substituted with one
5 or more alkyl, (hydroxy)alkyl, hydroxy, -C(O)NT⁷T⁸, cyano, oxo, -CO_tH, or
-CO_tT⁶; and
J* is hydrogen or alkyl.

9. A pharmaceutical composition comprising at least one compound of claim 1
10 together with a pharmaceutically acceptable vehicle or carrier therefor.

10. A method of treating T-cell mediated diseases which comprises administering
an effective amount of at least one compound claim 1 to a patient in need thereof.

15 11. A method of claim 10 wherein said T-cell mediated disorder is transplant
rejection.

12. A method of claim 10 wherein said T-cell mediated disorder is graft versus
host disease.

20 13. A method of claim 10 wherein said T-cell mediated disorder is rheumatoid
arthritis.

25 14. A method of claim 10 wherein said T-cell mediated disorder is multiple
sclerosis.

15. A method of claim 10 wherein said T-cell mediated disorder is juvenile
diabetes.

30 16. A method of claim 10 wherein said T-cell mediated disorder is asthma.

or R^{3a} and R^{4a} together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring;

R^{5a} is

- a) (phenyl)alkyl where the phenyl group is substituted with one or two alkoxy, alkoxycarbonyl, heteroaryl or -SO₂R^{8a};
- 5 b) optionally substituted (heteroaryl)alkyl; or
- c) optionally substituted (benzodioxole)alkyl;

R^{6a} is hydrogen;

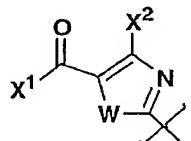
or R^{5a} and R^{6a} together with the nitrogen atom to which they are attached may combine to 10 form an optionally substituted heterocyclo ring; and

J* is hydrogen or alkyl.

8. A compound of claim 7 wherein

R^{1a} is hydrogen.

15 R^{2a} is



where W is O or S, X¹ is alkoxy, and X² is alkyl;

Z* is halogen, haloalkyl, oxazolyl, -NR^{3a}R^{4a}, -C(O)-N(H)-alkylene-COOH, or phenyl 20 optionally substituted with heteroaryl, CO_tH or CO_tT⁶;

R^{3a} is hydrogen;

20 R^{4a} is alkyl, alkoxy, optionally substituted (morpholinyl)alkyl, optionally substituted (pyrrolidinyl)alkyl, or optionally substituted (tetrahydrofuranyl)alkyl;

or R^{3a} and R^{4a} together with the nitrogen atom to which they are attached may combine to 25 form a piperazine, piperadine or morpholine ring optionally substituted with one or more alkyl, (hydroxy)alkyl, hydroxy, -C(O)NT⁷T⁸, cyano, oxo, -CO_tH, or -CO_tT⁶;

R^{5a} is

- a) (phenyl)alkyl where the phenyl group is substituted with one or more alkoxy, alkoxycarbonyl, heteroaryl, or -SO₂R^{8a};
- b) (tetrazolyl)alkyl, or (pyridyl)alkyl;

Z^* is halogen, alkyl, substituted alkyl, haloalkyl, $NR^{3a}R^{4a}$, $-C(O)-N(T^{10})-T^5-H$, $-C(O)-N(T^{10})-T^5-T^6$, optionally substituted aryl or optionally substituted heteroaryl;

R^{3a} is hydrogen or alkyl;

5 R^{4a} is alkyl, alkoxy, optionally substituted (heteroaryl)alkyl, optionally substituted heterocylo, optionally substituted (heterocyclo)alkyl, or (aryl)alkyl wherein the aryl group is substituted with one or two groups T^{1*} and T^{2*} and optionally further substituted with a group T^{3*} ;

or R^{3a} and R^{4a} together with the nitrogen atom to which they are attached may combine to
10 form an optionally substituted heterocyclo ring;

R^{5a} is optionally substituted (heteroaryl)alkyl, or (aryl)alkyl wherein the aryl group is substituted with one or two groups T^{1*} and T^{2*} and optionally further substituted with a group T^{3*} ;

or R^{5a} and R^{6a} together with the nitrogen atom to which they are attached may combine to
15 form an optionally substituted heterocyclo ring;

R^{6a} is hydrogen or alkyl;

J^* is hydrogen or alkyl;

T^{1*} and T^{2*} are independently alkoxy, alkoxy carbonyl, heteroaryl, SO_3H or $-SO_2R^{8a}$ where R^{8a} is alkyl, amino, alkylamino or dialkylamino;

20 or T^{1*} and T^{2*} together with the aryl ring to which they are attached may combine to form a bicyclic ring;

T^{3*} is H, alkyl, halo, haloalkyl or cyano.

7. A compound of claim 6 wherein

25 R^{1a} is H;

R^{2a} is thiazolyl, oxazolyl, tetrahydroindolinyl, or isoxazolyl any of which may be optionally substituted;

Z^* is halogen, alkyl, haloalkyl, $NR^{3a}R^{4a}$, $-C(O)-N(T^{10})-T^5-H$, or $-C(O)-N(T^{10})-T^5-T^6$;

R^{3a} is hydrogen;

30 R^{4a} is alkyl, alkoxy, haloalkyl, or optionally substituted (heterocyclo)alkyl;

or T⁷ and T⁸ together with the nitrogen atom to which they are attached combine to form a an optionally substituted heterocyclo ring;

or R⁵ and R⁶ together with the nitrogen atom to which they are attached combine to form

5 a heterocyclo ring selected from pyrrolidinyl, piperadiny, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), any of which are optionally independently substituted with one to three groups T^{1a}, T^{2a}, T^{3a} selected from alkyl optionally substituted with -T⁴NT⁷T⁸, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸,

10 where

T⁴ is a bond or -C(O)-;

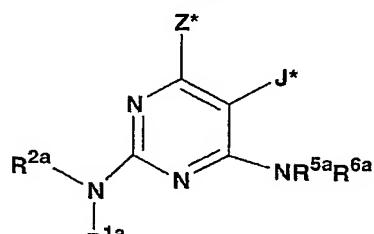
T⁵ is -C(O)-, -SO₂-, or -alkylene-C(O)O-;

T⁶ is alkyl, alkoxy, or heteroaryl;

15 T⁷ and T⁸ are independently H, alkyl, or cycloalkyl;

or T⁷ and T⁸ together with the nitrogen atom to which they are attached combine to form a an optionally substituted heterocyclo ring.

20 6. A compound of claim 1 of the following formula III



III

wherein

25 R^{1a} is H or alkyl;

R^{2a} is optionally substituted heteroaryl;

(d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl,

5

where

 T^4 is a bond, -SO₂-; or -C(O)-; T^5 is -SO₂-; or -alkylene-O-; T^6 is alkyl, or cycloalkyl;

10

 T^7 and T^8 are independently H or alkyl; and T^9 and T^{10} are hydrogen;

(e) alkyl optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} selected from -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or -T⁴-N(T¹⁰)-T⁵-T⁶

15

where

 T^4 is a bond; T^5 is -CO)-; T^6 is alkyl; T^7 and T^8 are independently H or alkyl; and

20.

 T^{10} is hydrogen;

(f) heterocyclo optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} selected from optionally substituted alkyl, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸

25

where

 T^4 is a bond or -C(O)-; T^5 is -C(O)-, -SO₂-; or -alkylene-C(O)O-; T^6 is alkyl, alkoxy, or heteroaryl; T^7 and T^8 are independently H, alkyl, or cycloalkyl;

T^6 is alkyl, alkoxy, or heteroaryl;
 T^7 and T^8 are independently H, alkyl, or cycloalkyl;
 or T^7 and T^8 together with the nitrogen atom to which they are
 attached combine to form a an optionally substituted
 heterocyclo ring;

5

R^5 is hydrogen or alkyl;

R^6 is

- (a) hydrogen;
- (b) (aryl)alkyl where the aryl group is optionally independently substituted with
 one or more groups T^{1c} , T^{2c} , T^{3c} selected from optionally substituted alkyl,
 halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶,
 -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo,
 or heteroaryl

where

15

T^4 is a bond, -SO₂-; or -C(O)-;

T^5 is -SO₂-; or -alkylene-O-;

T^6 is alkyl, or cycloalkyl;

T^7 and T^8 are independently H or alkyl; and

T^9 and T^{10} are hydrogen;

20

- (c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶,
 -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸,
 -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl,

25

where

T^4 is a bond, -SO₂-; or -C(O)-;

T^5 is -SO₂-; or -alkylene-O-;

T^6 is alkyl, or cycloalkyl;

T^7 and T^8 are independently H or alkyl; and

30

T^9 and T^{10} are hydrogen;

(e) alkyl optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} selected from -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or -T⁴-N(T¹⁰)-T⁵-T⁶

where

5 T⁴ is a bond;

 T⁵ is -CO)-;

 T⁶ is alkyl;

 T⁷ and T⁸ are independently H or alkyl; and

 T¹⁰ is hydrogen;

10 (f) heterocyclo optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} selected from optionally substituted alkyl, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸,

 where

15 T⁴ is a bond or -C(O)-;

 T⁵ is -C(O)-, -SO₂-, or -alkylene-C(O)O-;

 T⁶ is alkyl, alkoxy, or heteroaryl;

 T⁷ and T⁸ are independently H, alkyl, or cycloalkyl;

 or T⁷ and T⁸ together with the nitrogen atom to which they are

20 attached combine to form a an optionally substituted heterocyclo ring;

 or R³ and R⁴ together with the nitrogen atom to which they are attached combine to form a heterocyclo ring selected from pyrrolidinyl, piperadiny, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), any of which are optionally independently substituted with one to three groups T^{1a} , T^{2a} , T^{3a} selected from alkyl optionally substituted with -T⁴NT⁷T⁸, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸,

 where

30 T⁴ is a bond or -C(O)-;

 T⁵ is -C(O)-, -SO₂-, or -alkylene-C(O)O-;

halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl

where

5

T⁴ is a bond, -SO₂-; or -C(O)-;

T⁵ is -SO₂-; or -alkylene-O-;

T⁶ is alkyl, or cycloalkyl;

T⁷ and T⁸ are independently H or alkyl; and

T⁹ and T¹⁰ are hydrogen;

10

(c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl

15

where

T⁴ is a bond, -SO₂-; or -C(O)-;

T⁵ is -SO₂-; or -alkylene-O-;

T⁶ is alkyl, or cycloalkyl;

T⁷ and T⁸ are independently H or alkyl; and

T⁹ and T¹⁰ are hydrogen;

20

(d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl

25

where

T⁴ is a bond, -SO₂-; or -C(O)-;

T⁵ is -SO₂-; or -alkylene-O-;

T⁶ is alkyl, or cycloalkyl;

T⁷ and T⁸ are independently H or alkyl; and

T⁹ and T¹⁰ are hydrogen;

30

where

T^4 is a bond or $-C(O)-$;

T^5 is $-C(O)-$, or $-C(O)O-$;

T^6 is alkyl or haloalkyl;

5 T^7 and T^8 are independently

H;

10 alkyl optiontinally substituted with cycloalkyl, heteroaryl,

hydroxy or $-NT^7T^8$;

cycloalkyl; or

aryl optionally substituted with halogen;

or T^7 and T^8 together with the nitrogen atom to which they are

attached combine to form a heterocyclo ring optionally

substituted with (hydroxy)alkyl, CO_tH or CO_tT^6

15 T^{10} is hydrogen;

(d) alkyl optionally substituted with one or more $-OH$, $-CO_tH$, $-CO_tT^6$, $-T^4-NT^7T^8$,

$-T^4-N(T^{10})-T^5-H$, or ; $-T^4-N(T^{10})-T^5-T^6$

where

T^4 is $-C(O)-$;

T^5 is -alkylene-O-;

20 T^6 is alkyl;

T^7 and T^8 are independently H, alkyl, cycloalkyl, aryl, (aryl)alkyl

optionally substituted as described in the definition of R^4 ,

or heterocyclo optionally substituted as described in the

definition of R^3 and R^4 combining to form a heterocyclo

25 ring; and

T^{10} is H;

R^3 is H or alkyl optionally substituted with one or more $-OH$, or $-OT^6$;

R^4 is

(a) hydrogen;

30 (b) (aryl)alkyl where the aryl group is optionally independently substituted with
one or more groups T^{1a} , T^{2a} , T^{3a} selected from optionally substituted alkyl,

alkyl optiontinally substituted with cycloalkyl, heteroaryl,
hydroxy or -NT⁷T⁸;
cycloalkyl; or
aryl optionally substituted with halogen;
or T⁷ and T⁸ together with the nitrogen atom to which they are
attached combine to form a heterocyclo ring optionally
substituted with (hydroxy)alkyl, CO_tH or CO_tT⁶
T¹⁰ is hydrogen;

5

(c) alkyl optionally substituted with one or more -OH, -CO_tH, -CO_tT⁶, -T⁴-NT⁷T⁸,
-T⁴-N(T¹⁰)-T⁵-H, or ; -T⁴-N(T¹⁰)-T⁵-T⁶

10

where

T⁴ is -C(O)-;

T⁵ is -alkylene-O-;

T⁶ is alkyl;

15

T⁷ and T⁸ are independently H, alkyl, cycloalkyl, aryl, (aryl)alkyl
(optionally substituted as described in the definition of R⁴),
or heterocyclo (optionally substituted as described in the
definition of R³ and R⁴ combining to form a heterocyclo
ring); and

20

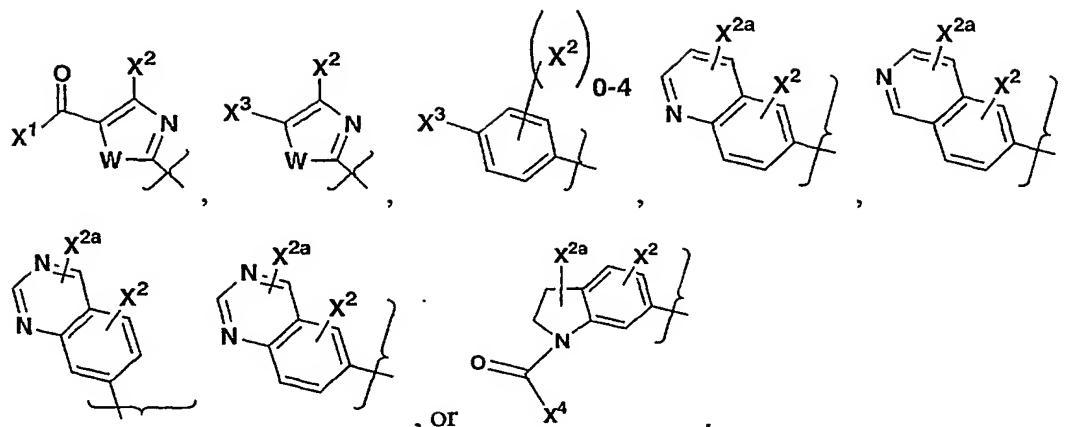
T¹⁰ is H;

J is

- (a) H, or
- (b) alkyl or alkenyl either of which may be optionally substituted with one or
more -OH, -OT⁶, -CO_tH, or -CO_tT⁶, where T⁶ is alkyl;

25 L is

- (a) H;
- (b) halogen, alkoxy, haloalkyl, -NR⁵R⁶, -C(O)OR^{4b}, -C(O)NR⁵R⁶;
- (c) aryl or heteroaryl either of which may be optionally substituted with one or
more T^{1c}, T^{2c}, T^{3c} selected from cyano, optionally substituted alkyl,
(hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -SO_tT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸,
-T⁴N(T¹⁰)-T⁵-T⁶ or heteroaryl,



wherein:

- 5 W is O or S;
- X¹ is NHT⁸ or OT⁶;
- X² and X^{2a} are independently hydrogen, halo, OT⁶, alkyl, or haloalkyl;
- X³ is heteroaryl (preferably, pyrimidinyl, imidazolyl, oxazolyl, or thiazolyl any of which may be further optionally substituted), cyano, C(O)_tT⁶, or S(O)_tNT⁷T⁸; and
- 10 X⁴ is alkyl, haloalkyl, NHT⁸ or OT⁶.

5. A compound of claim 4 wherein

Z is

- (a) halogen, or -NR³R⁴; or
- 15 (b) aryl or heteroaryl either of which may be optionally substituted with one or more T^{1a}, T^{2a}, T^{3a} selected from cyano, optionally substituted alkyl, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -SO_tT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸, or -T⁴N(T¹⁰)-T⁵-T⁶,

where

- 20 T⁴ is a bond or -C(O)-;
- T⁵ is -C(O)-, or -C(O)O-;
- T⁶ is alkyl or haloalkyl;
- T⁷ and T⁸ are independently
- H;

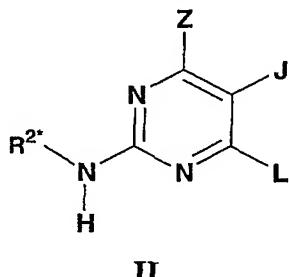
substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl;

(e) alkyl optionally independently substituted with one or more groups T^{1c} , T^{2c} ,
 5 T^{3c} selected from -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or
 -T⁴-N(T¹⁰)-T⁵-T⁶;

(f) heterocyclo optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} selected from optionally substituted alkyl, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸:

or R⁵ and R⁶ together with the nitrogen atom to which they are attached combine to form a heterocyclo ring selected from pyrrolidinyl, piperadiny, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), any of which are optionally independently substituted with one to three groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸.

4. A compound of claim 1 having formula II



where:

R^{2*} is

-CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl;

(e) alkyl optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from -OH, -OT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸ or -T⁴-N(T¹⁰)-T⁵-T⁶;

(f) heterocyclo optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸;

10 or R³ and R⁴ together with the nitrogen atom to which they are attached combine to form a heterocyclo ring selected from pyrrolidinyl, piperadiny, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), any of which are optionally independently substituted with one to three groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, optionally substituted aryl, cyano, -OH, -OT⁶, -CO_tH, -CO_tT⁶, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T⁴-N(T¹⁰)-T⁵-T⁶, or -T⁴-NT⁷T⁸;

R⁵ is hydrogen or alkyl;

R⁶ is

(a) hydrogen;

20 (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl;

25 (c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl;

30 (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1c}, T^{2c}, T^{3c} selected from optionally

(hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -SO_tT⁶, -CO_tH, -CO_tT⁶, -T⁴NT⁷T⁸, -T⁴N(T¹⁰)-T⁵-T⁶ or heteroaryl;

(d) alkyl optionally substituted with one or more -OH, -CO_tH, -CO_tT⁶, -T⁴-NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-H, or ; -T⁴-N(T¹⁰)-T⁵-T⁶;

5 R¹ is H or alkyl;

R² is

(a) thiazolyl or oxazolyl each optionally substituted with one to three groups T¹, T², T³, selected from alkyl, haloalkyl, halo, heteroaryl, cyano, C(O)_tT⁶, OT⁶, or -T⁴NT⁷T⁸;

10 (b) aryl substituted with one to three groups T¹, T², T³ selected from optionally substituted heteroaryl, cyano, C(O)_tT⁶, S(O)_tN(T⁹)T⁶, halo alkyl, or haloalkyl; or

15 (c) aryl fused to a heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T¹, T², T³ selected from halo, OH, OT⁶, alkyl, -CO_tH, -CO_tT⁶, or -C(O)NT⁷T⁸;

R³ is H or alkyl optionally substituted with one or more -OH, or -OT⁶;

R⁴ is

(a) hydrogen;

(b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl;

20 (c) (heteroaryl)alkyl where the heteroaryl group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶, -CO_tH, -CO_tT⁶, -SO₃H, -SO_tT⁶, -SO_tN(T⁹)(T⁶), -T⁴NT⁷T⁸, -T⁴-N(T¹⁰)-T⁵-T⁶, heterocyclo, or heteroaryl;

25 (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1a}, T^{2a}, T^{3a} selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT⁶, -ST⁶,

30

- (c) (heteroaryl)alky where the heteroaryl group is optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} ;
 - (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} ;
 - 5 (e) alkyl optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} ;
 - (f) heterocyclo optionally independently substituted with one or more groups T^{1c} , T^{2c} , T^{3c} ;
- or R^5 and R^6 together with the nitrogen atom to which they are attached combine to form
10 a 4 to 8-membered heterocyclo ring optionally substituted with one to three groups T^{1c} , T^{2c} , T^{3c} .

3. A compound of claim 2 wherein

Z is

- 15 (a) halogen, alkoxy, haloalkyl, $-NR^3R^4$, $-C(O)OR^4$, $-C(O)NR^3R^4$;
- (b) aryl or heteroaryl either of which may be optionally substituted with one or
more T^{1a} , T^{2a} , T^{3a} selected from cyano, optionally substituted alkyl,
(hydroxy)alkyl, $-OH$, $-OT^6$, $-ST^6$, $-SO_tT^6$, $-CO_tH$, $-CO_tT^6$, $-T^4NT^7T^8$,
 $-T^4N(T^{10})-T^5-T^6$ or heteroaryl;
- 20 (c) alkyl optionally substituted with one or more $-OH$, $-CO_tH$, $-CO_tT^6$, $-T^4NT^7T^8$,
 $-T^4-N(T^{10})-T^5-H$, or ; $-T^4-N(T^{10})-T^5-T^6$;

J is

- (a) H, or
- (b) alkyl or alkenyl either of which may be optionally substituted with one or
more $-OH$, $-OT^6$, $-CO_tH$, or $-CO_tT^6$;

L is

- (a) H;
- (b) halogen, alkoxy, haloalkyl, $-NR^5R^6$, $-C(O)OR^{4b}$, $-C(O)NR^5R^6$;
- (c) aryl or heteroaryl either of which may be optionally substituted with one or
more T^{1c} , T^{2c} , T^{3c} selected from cyano, optionally substituted alkyl

(c) aryl or heteroaryl either of which may be optionally substituted with one or more T^{1a} , T^{2a} , T^{3a} ; or

(d) optionally substituted alkyl;

R^1 is H or alkyl;

5 R^2 is

(a) heteroaryl optionally substituted with one to three groups T^1 , T^2 , T^3 ;

(b) aryl substituted with one to three groups T^1 , T^2 , T^3 ; or

(c) aryl fused to a heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T^1 , T^2 , T^3 ;

10 R^3 is H or optionally substituted alkyl;

R^4 is

(a) hydrogen;

(b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} ;

15 (c) (heteroaryl)alkyl where the heteroaryl group is optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} ;

(d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T^{1a} , T^{2a} , T^{3a} ;

(e) alkyl optionally independently substituted with one or more groups T^{1a} , T^{2a} ,
20 T^{3a} ;

(f) heterocyclo optionally independently substituted with one or more groups T^{1a} ,
 T^{2a} , T^{3a} ;

or R^3 and R^4 together with the nitrogen atom to which they are attached combine to form
a 4 to 8-membered heterocyclo ring optionally substituted with one to three
groups T^{1a} , T^{2a} , T^{3a} ;

25 R^5 is hydrogen or alkyl;

R^6 is

(a) hydrogen;

(b) (aryl)alkyl where the aryl group is optionally independently substituted with
one or more groups T^{1c} , T^{2c} , T^{3c} ;

30

- (1) are each independently hydrogen or a group provided in the definition of T⁶,
or
5 (2) T⁷ and T⁸ may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T^{1-1c}, T^{2-2c} and T^{3-3c}, or
10 (3) T⁷ or T⁸, together with T⁹, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T^{1-1c}, T^{2-2c} and T^{3-3c}, or
(4) T⁷ and T⁸ or T⁹ and T¹⁰ together with the nitrogen atom to which they are attached may combine to form a group -N=CT¹³T¹⁴ where T¹³ and T¹⁴ are each independently H or a group provided in the definition of T⁶; and
15 T¹¹ and T¹² are each independently
(1) a single bond,
(2) alkylene,
(3) alkenylene, or
(4) alkynylene.

20 2. A compound of claim 1 wherein

Z is

- (a) halogen, alkoxy, haloalkyl, -NR³R⁴, -C(O)OR⁴, -C(O)NR³R⁴;
(b) aryl or heteroaryl either of which may be optionally substituted with one or
25 more T^{1a}, T^{2a}, T^{3a};
(c) optionally substituted alkyl;

J is

- (a) H, or
(b) alkyl or alkenyl either of which may be optionally substituted;

L is

- 30 (a) H;
(b) halogen, alkoxy, haloalkyl, -NR⁵R⁶, -C(O)OR^{4b}, -C(O)NR⁵R⁶;

aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl;

(ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or

5 (iii) a group (i) or (ii) which is independently substituted by one or more (preferably 1 to 3) of the following groups (2) to (13) of the definition of T^{1-1c} , T^{2-2c} and T^{3-3c} ,

(2) $-OH$ or $-OT^6$,

(3) $-SH$ or $-ST^6$,

10 (4) $-C(O)_tH$, $-C(O)_tT^6$, or $-O-C(O)T^6$, where t is 1 or 2;

(5) $-SO_3H$, $-S(O)_tT^6$, or $S(O)_tN(T^9)T^6$,

(6) halo,

(7) cyano,

(8) nitro,

15 (9) $-T^4-NT^7T^8$,

(10) $-T^4-N(T^9)-T^5-NT^7T^8$,

(11) $-T^4-N(T^{10})-T^5-T^6$,

(12) $-T^4-N(T^{10})-T^5-H$,

(13) oxo,

20 T^4 and T^5 are each independently

(1) a single bond,

(2) $-T^{11}-S(O)_rT^{12}-$,

(3) $-T^{11}-C(O)-T^{12}-$,

(4) $-T^{11}-C(S)-T^{12}-$,

25 (5) $-T^{11}-O-T^{12}-$,

(6) $-T^{11}-S-T^{12}-$,

(7) $-T^{11}-O-C(O)-T^{12}-$,

(8) $-T^{11}-C(O)-O-T^{12}-$,

(9) $-T^{11}-C(=NT^{9a})-T^{12}-$, or

30 (10) $-T^{11}-C(O)-C(O)-T^{12}-$

T^7 , T^8 , T^9 , T^{9a} and T^{10}

(b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T^{1c}, T^{2c} or T^{3c};

R³ and R⁴ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T^{1a}, T^{2a} or T^{3a};

5 or R³ and R⁴ together with the nitrogen atom to which they are attached may combine to form a 4 to 8 membered heterocyclo ring optionally substituted with one to three groups T^{1a}, T^{2a} or T^{3a};

10 R^{4a} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocyclo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T^{1b}, T^{2b} or T^{3b};

R^{4b} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocyclo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be 15 optionally substituted with one to three groups T^{1c}, T^{2c} or T^{3c};

R^{4c} and R^{4d} are independently alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T^{1a}, T^{2a} or T^{3a};

20 R⁵ and R⁶ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally independently substituted where valance allows with one to three groups T^{1c}, T^{2c} or T^{3c};

or R⁵ and R⁶ together with the nitrogen atom to which they are attached may combine to 25 form a 4 to 8-membered heterocyclo ring optionally substituted with one to three groups T^{1c}, T^{2c} or T^{3c};

T^{1-1c}, T^{2-2c}, and T^{3-3c} are each independently

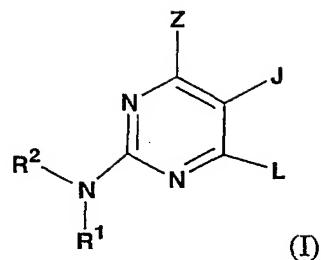
(1) hydrogen or T⁶, where T⁶ is

(i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl,

30

We claim:

1. A compound of Formula I



5

wherein

R¹ is H or alkyl;

R² is

- 10 (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T¹, T², T³;
 (b) aryl substituted with one to three groups T¹, T², T³ provided that at least one of T¹, T², T³ is other than H; or
 (c) aryl fused to a heteroaryl or heterocyclo ring wherein the combined ring
 15 system may be optionally substituted with one to three groups T¹, T², T³;

Z is

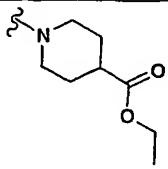
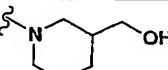
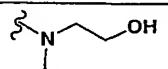
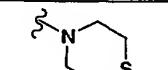
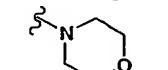
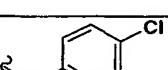
- (a) -OR⁴, -C(O)R⁴, -C(O)OR⁴, -SR⁴, -NR³R⁴, -C(O)NR³R⁴, -NR³SO₂R^{4c} halogen, nitro, haloalkyl; or
 (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be
 20 optionally substituted with one to three groups T^{1a}, T^{2a} T^{3a};

J is

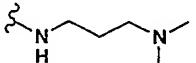
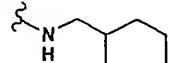
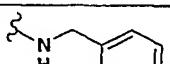
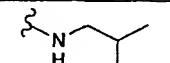
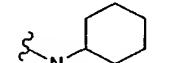
- (a) hydrogen, halo, -OR^{4a}, or
 (b) alkyl, alkenyl, or alkynyl any of which may be optionally substituted with one to three groups T^{1b}, T^{2b} or T^{3b};

25 L is

- (a) hydrogen, -OR^{4b}, -C(O)R^{4b}, -C(O)OR^{4b}, -SR^{4b}, -NR⁵R⁶, -C(O)NR⁵R⁶, -NR⁵SO₂R^{4d}, halogen, haloalkyl, nitro, or

M8		2-[4-[4-(4-Ethoxycarbonylpyperidine-1-carbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	83	1.78	623
M9		2-[4-[4-(3-Hydroxymethyl-piperidine-1-carbonyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	79	1.54	581
M10		2-[4-[4-(N-2-Hydroxyethyl-N-ethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	74	1.51	555
M11		2-[4-[4-(Thiomorpholine-1-carbonyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	77	1.74	569
M12		2-[4-[4-(Morpholine-1-carbonyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	86	1.57	553
M13		2-[4-[4-(4-Chlorophenylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	13	2.08	593

^aHPLC conditions used to determine retention times: 2 min gradient 0-100% B in A (A; 5mM NH₄OAc in 90/10 water/acetonitrile; B; 5mM NH₄OAc in 10/90 water/acetonitrile) using a Primesphere C4 4.6 x 30 mm column at 254 nm.

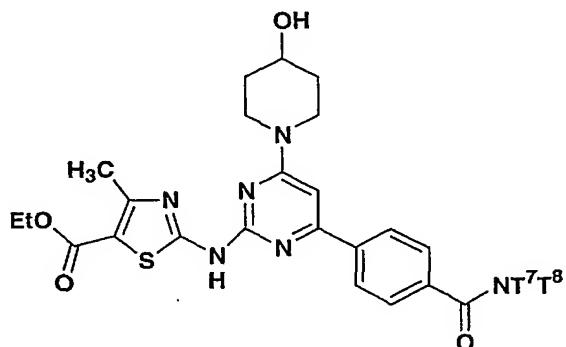
		acid ethyl ester			
M2		2-[4-[4-(3-Dimethylamino-propylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	92	1.48	568
M3		2-[4-[4-(Cyclohexylmethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	9	2.01	579
M4		2-[4-[4-(Pyridin-4-ylmethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	79	1.55	574
M5		2-[4-[4-(Isobutylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	47	1.79	539
M6		2-[4-[4-(N-Cyclohexyl-N-methylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	91	1.97	579
M7		2-[4-[4-(N-Cyclopropylmethyl-N-propylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	96	1.98	579

				yl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, methyl amide		
--	--	--	--	---	--	--

^aHPLC conditions used to determine retention times; 4 min gradient 0-100% B in A(A; 0.1% TFA in 90/10 water/methanol; B; 0.1%TFA in 10/90 water/methanol) using a YMC turbopack column at 254 nm. ^bYMC ODS 5 μ m C18 column 4.6 x 30 mm (2 min).

5

Example M1-M13



Examples M1 to M13 were prepared in the following manner using the appropriate amines:

A solution of F1 (425 mg in 17 mL DMF) was dispensed into vials. To each vial was added the appropriate amines (155 μ L, 0.5M in DMF, 1.5 equiv.), EDAC/HOBT (40 μ L, 0.25M in DMF, 2 equiv.) followed by diisopropylethylamine (27 μ L, 3 equiv.). The reactions were stirred at room temperature overnight. Purification by preparative HPLC (C₁₈, water/acetonitrile containing 5mM NH₄OAc) afforded the desired products.

Table M

Ex.	NT ⁷ T ⁸	Name	Yield, %	HPLC Retention ^a (min)	MS Reported
M1		2-[4-[4-(2-Diisopropylaminoethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid, methyl amide	80	1.60	610



Examples **L4** to **L5** were prepared in a similar manner to that used for Example
5 **L1** utilizing the appropriate replacement for ethyl 2-chloro-4,4,4,-trifluoroacetoacetate in
step **L1.4**.

Table L

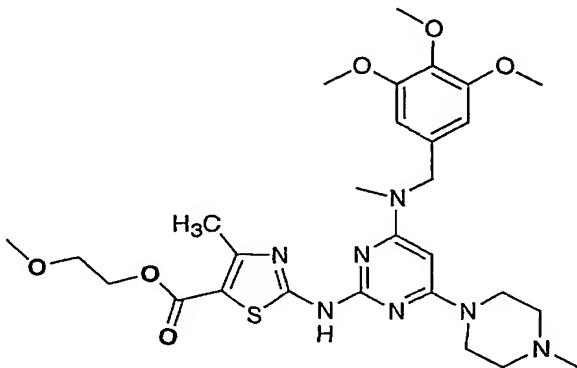
Ex.	Z	L	R ²	Name	HPLC Retention ^a (min)	MS Reported
L4				2-[[4-[4-Hydroxypiperidin-1-yl]-6-[N-methyl][[N-[(3,4,5-trimethoxyphenyl)methyl][N-methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, butyl ester	1.56 ^b	600.54
L5				2-[[4-[1-morpholinyl]-6-[[2-[1-morpholinyl]ethyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, butyl ester	1.30 ^b	506.32
L6				2-[[4-[4-methyl-1-piperazinyl]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-isopropyl-5-thiazolecarboxylic acid, ethyl ester	3.07	600.16
L7				2-[[4-[4-methyl-1-piperazinyl]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]	2.00	557.61

A mixture of **L1.3** (30 mg, 0.065 mmol, 1.0 eq) and 2-chloroacetoacetonitrile (prepared from 5-methyl-isoxazole by the method of Blount *et al.* *J. Org. Chem.* **1978**, **43**, 3821) (8.0 mg, 0.0682 mmol, 1.05 eq) in ethanol (0.5 mL) was heated in a sealed tube at 80 °C. After 7 h, the reaction mixture was cooled to rt, and the precipitated solid was 5 collected by filtration, washed with ether and dried. Gave 23 mg (63% yield) of **L2** as the HCl salt. Off-white solid; LC/MS: 525.22 [M+H]⁺; HPLC: 87 % at 1.28 min (Xterra 5 μm C18 column 4.6 x 30 mm, 10-90 % aqueous methanol over 2 min containing 0.2% H₃PO₄, 5 mL/min, monitoring at 254 nm).

10

Example L3

2-[[4-[4-Methylpiperazin-1-yl]-6-methyl-6-[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, 2-methoxyethyl ester



15

L3

A mixture of **L1.3** (50 mg, 0.108 mmol, 1.0 eq) and 2-chloro-3-oxo-butyric acid 2-methoxy-ethyl ester (21.2 mg, 0.108 mmol, 1.0 eq) in ethanol (0.5 mL) was heated in a sealed tube at 100 °C. After 1.5 h, the reaction mixture was cooled to rt and methyl *t*-butyl ether (1ml) was added. The precipitated solid was collected by filtration, washed 20 with methyl *t*-butyl ether and dried to afford 42.8 mg (62% yield) of product as the HCl salt. Beige solid; LC/MS: 602.20 [M+H]⁺; HPLC: 92.8 % at 1.24 min (Xterra 5 μm C18 column 4.6 x 30 mm, 10-90 % aqueous methanol over 2 min containing 0.2% H₃PO₄, 5 mL/min, monitoring at 254 nm).

Example L4-15

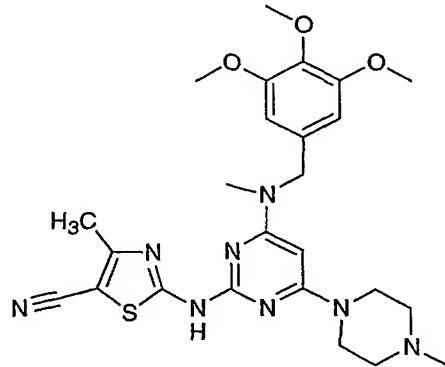
afford 299 mg (79% yield) of product as an off-white solid. LC/MS: 462.47 [M+H]⁺; HPLC: >95 % at 1.98 min (YMC ODS 5 μ m C18 column 4.6 x 50 mm, 10-90 % aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm).

5 L1.4; 2-[4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-trifluoromethyl-5-thiazolecarboxylic acid, ethyl ester

A mixture of L1.3 (30 mg, 0.065 mmol, 1.0 eq) and ethyl 2-chloro-4,4,-
10 trifluoroacetoacetate (90%, 15.8 mg, 0.065, 1.0 eq) in ethanol (0.5 mL) was heated in a sealed tube at 100 °C. After 19 h, the mixture was cooled to rt, poured into saturated NaHCO₃ (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by preparative TLC (0.5 mm, 5% methanol/dichloromethane, eluted 2x) to afford 14.6
15 mg (36% yield) of L1 as a glass. LC/MS: 626.19 [M+H]⁺; HPLC: >95 % at 1.51 min (Xterra 5 μ m C18 column 4.6 x 30 mm, 10-90 % aqueous methanol over 2 min containing 0.2% H₃PO₄, 5 mL/min, monitoring at 254 nm).

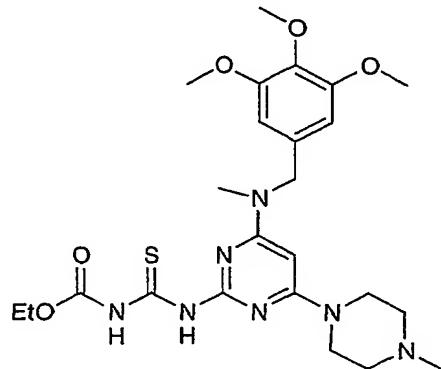
Example L2

20 2-[4-[4-Methylpiperazin-1-yl]-6-[N-methyl-N-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-cyanothiazole



L2

L1.2; 2-[Ethoxycarbonylaminothiocarbonylamino]-4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-[3,4,5-trimethoxyphenyl]methyl]pyrimidine

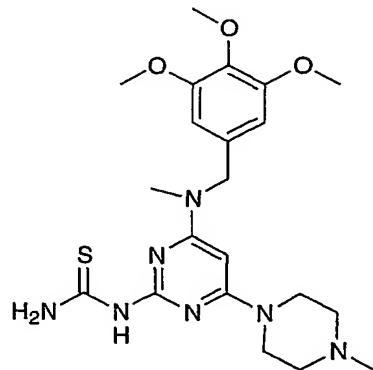


5

L1.2

A solution of **L1** (0.5 g) and ethyl isothiocyanatoformate (0.15 mL, 1.242 mmol) in 1,4-dioxane (5 mL) was heated at reflux for 1.5 h during which time a solid formed. The reaction mixture was cooled and the solid was collected by filtration, washed with ether and dried to afford 445 mg (67% yield) of **L1.2** as a beige solid. LC/MS: 534.55 [M+H]⁺; HPLC: 100 % at 2.31 min (YMC ODS 5 μ m C18 column 4.6 x 50 mm, 10-90 % aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm).

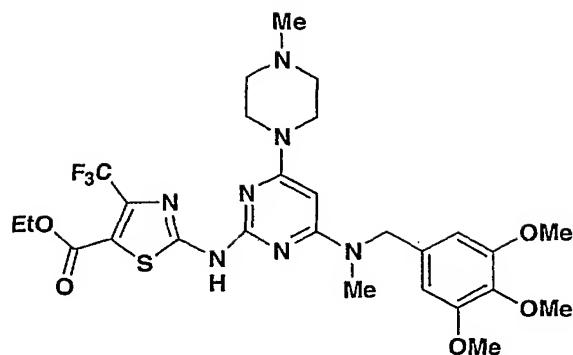
L1.3; 2-[Aminothiocarbonylamino]-4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-[3,4,5-trimethoxyphenyl]methyl]pyrimidine



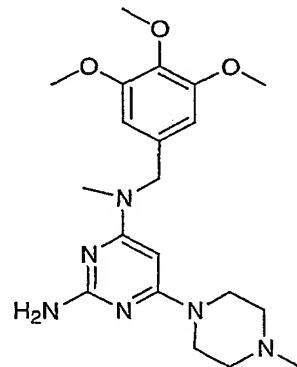
15

L1.3

A solution of **L1.2** (438 mg, 0.821 mmol, 1.0 eq) in 2 N NaOH (8 mL) was stirred at rt for 19 h and then heated at reflux for 15 min. The reaction mixture was cooled in an ice/water bath and the solid was collected by filtration, washed with water and dried to



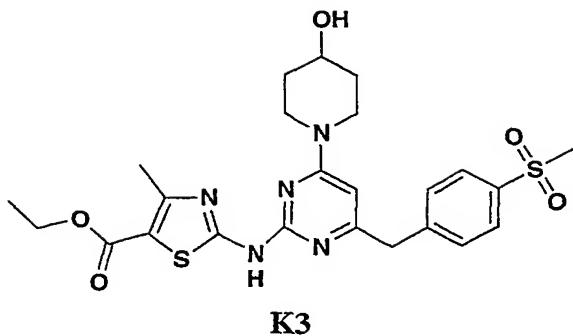
L1.1; 2-Amino-4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-[3,4,5-trimethoxyphenyl]methyl]pyrimidine



5

L1.1

A mixture of 2-amino-4,6-dichloropyrimidine (1.5 g, 9.146 mmol, 1.0 eq), N-methyl-3,4,5-trimethoxybenzylamine (2.03 g, 9.604 mmol, 1.05 eq), and diisopropylethylamine (4.8 mL, 27.438 mmol, 3.0 eq) in n-butanol (20 mL) was heated in a sealed tube at 110 °C for 43 h. After cooling to rt, N-methylpiperazine (1.52 mL, 13.719 mmol, 1.5 eq) was added. The reaction mixture was heated at 125 °C for 48 h, and then cooled and concentrated *in vacuo*. The residue was passed through a plug of silica gel using 5% methanol/dichloromethane to provide **L1.1** a tan semi-solid which was used in subsequent reactions without further purification. LC/MS: 403.59 [M+H]⁺; HPLC: 90 % at 1.42 min (YMC ODS 5 µm C18 column 4.6 x 50 mm, 10-90 % aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm).



5

10

To a solution of **K2** (28 mg, 0.054 mmol) in dichloromethane (2 mL) was added peracetic acid (32% solution in acetic acid, 50 μ L, 0.233 mmol) and the mixture was 15 stirred at 23°C for half an hour after which HPLC analysis indicated no trace of starting material. Dimethylsulfide was added and the mixture was concentrated. The residue was stripped 2 times with methanol, triturated with ethyl acetate to give **K3** as a light yellow 20 solid (21 mg, 72%). $^1\text{H-NMR}$ (CD_3OD) δ : 7.94 (2H, d, $J = 8$ Hz), 7.64 (2H, d, $J = 8$ Hz), 6.51 (1H, s), 4.34 (2H, q, $J = 7$ Hz), 4.27 (2H, m), 4.08 (2H, s), 4.00 (1H, m), 3.57 (2H, m), 3.12 (3H, s), 2.58 (3H, s), 2.02 (2H, m), 1.62 (2H, m), 1.38 (3H, t, $J = 7$ Hz). HPLC: 91.1%, ret. time = 1.586 min., LC/MS ($M+\text{H}^+$) = 532.

Example L1

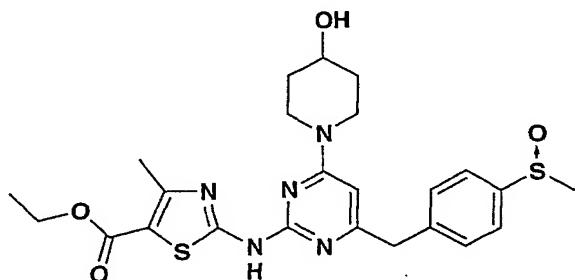
25 2-[4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-[(3,4,5-trimethoxyphenyl)methyl]aminol-2-pyrimidinylamino]-4-trifluoromethyl-5-thiazolecarboxylic acid, ethyl ester

J = 7 Hz), 4.10 (2H, m), 3.78 (3H, m), 3.31 (1H, Merge with H₂O), 3.17 (1H, d, *J* = 5 Hz), 2.50 (3H, merge with DMSO), 2.44 (3H, s), 1.79 (2H, m), 1.37 (2H, m), 1.29 (3H, t, *J* = 7 Hz). HPLC: 100%, ret. time = 1.720 min., LC/MS (M+H)⁺ = 500.

5

Example K2

2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methanesulfinyl-benzyl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester



10

K2

To a solution of **K1** (43 mg, 0.086 mmol) in dichloromethane (3 mL) was added peracetic acid (32% solution in acetic acid, 24 μ L, 0.112 mmol) and the mixture was stirred at 23°C for half an hour after which HPLC analysis indicated no trace of starting material. Dimethylsulfide was added and the mixture was concentrated. The residue which crystallized from methanol gave pure **K2** as a cream solid (44 mg, 100%). ¹H-NMR (DMSO-d₆) δ : 11.58 (1H, br, s), 7.92 (2H, d, *J* = 8 Hz), 7.68 (2H, d, *J* = 8 Hz), 6.63 (1H, s), 4.86 (1H, br, s), 4.28 (2H, q, *J* = 7 Hz), 4.00 (5H, m), 2.76 (3H, s), 2.56 (3H, merge with DMSO), 1.98 (2H, s), 1.86 (2H, m), 1.44 (2H, m), 1.35 (3H, t, *J* = 7 Hz).

15

HPLC: 91.3%, ret. time = 1.270 min., LC/MS (M+H)⁺ = 516.

20

Example K3

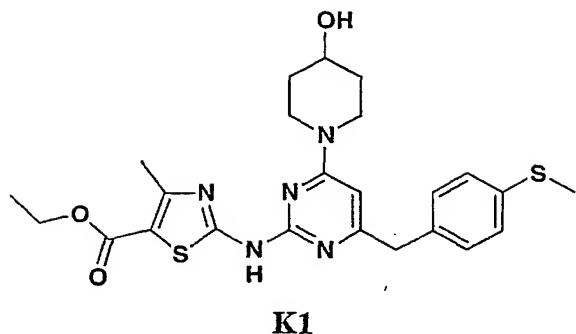
2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methanesulfonyl-benzyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

To a solution of **K1.1** (0.3 g, 1.21 mmol) in dry dioxane (20 mL) was added ethyl isothiocyanatoformate (0.143 mL, 1.21 mmol). The reaction mixture was heated in an oil bath at 120°C for 1 hour and then concentrated to dryness to give an orange paste. The residue was then dissolved in aqueous sodium hydroxide (1N, 15 mL) and heated to 80°C
5 for 1 hour. The reaction mixture was allowed to cool to room temperature, the pH adjusted to 7 with aqueous HCl and the solid which precipitated out was collected by filtration and dried under vacuum. The thiourea was then suspended in ethanol and 2-chloroacetoacetate (0.130 mL, 0.92 mmol), and the resulting mixture was maintained at 100°C for 3 hours, cooled down to room temperature and diluted with water. The
10 resulting off-white solid was collected by filtration and vacuum dried. The solid was finally added to phosphorous oxychloride (5 mL) and stirred at 85°C for 3 hours and then it was cooled down to room temperature and poured into 50g of ice. After the ice melted, the aqueous phase was extracted with a 7:3 mixture of ethyl acetate/THF. The organic phase was dried with sodium sulphate, filtered and concentrated. The residue was
15 purified on flash chromatographiy with ethyl acetate to give a yellow solid which was triturated with methanol to give pure **K1.2** (0.108 g, 20%). $^1\text{H-NMR}$ (DMSO-d₆) δ: 12.45 (1H, br s) 7.26 (5H, m), 4.27 (2H, q, J = 7 Hz), 4.05 (2H, s) 2.54 (3H, s), 2.44 (3H, s), 1.32 (3H, t, J = 7 Hz). HPLC: 95.8%, ret. time = 2.350 min., LC/MS (M+H)⁺ = 435.

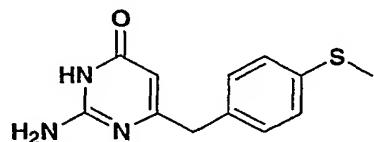
20

K1.3: 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methylsulfanyl-benzyl)-pyrimidin-2-ylaminol]-4-methyl-5-thiazolecarboxylic acid ethyl ester

A solution of **K1.2** (95 mg, 0.21 mmol) and 4-hydroxypiperidine (26 mg, 0.26 mmol) in N-methylpyrrolidinone (3.0 mL) was heated to 60°C for an hour. An additional portion of 4-hydroxypiperidine (26 mg, 0.26 mmol) was added and the mixture was stirred for 15 minutes. The reaction mixture was allowed to cool to room temperature, diluted with water and extracted with ethyl acetate. The organic phase was washed with water, brine, dried with magnesium sulphate, filtered and concentrated. The residue was purified on flash chromatography using ethyl acetate to give **K1** which crystallized from methanol (98 mg, 93%). $^1\text{H-NMR}$ (DMSO-d₆) δ: 11.49 (1H, s), 7.29 (2H, d, J = 8 Hz), 7.19 (2H, d, J = 8 Hz), 6.47 (1H, s), 4.79 (1H, d, J = 4 Hz), 4.22 (2H, q,
25
30

**K1.1: 2-Amino-6-(4-methylsulfanyl-benzyl)-3H-pyrimidin-4-one**

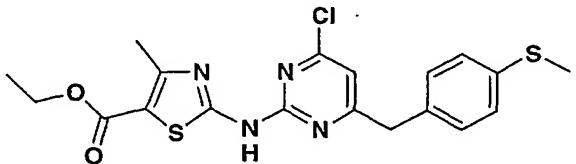
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**K1.1**

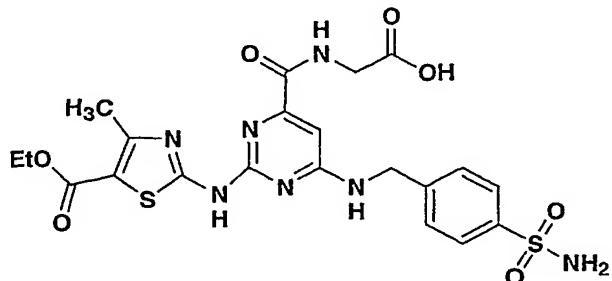
A solution of guanidine carbonate (0.785 g, 4.36 mmol), 4-(4-methylsulfanyl-
10 phenyl)-3-oxo-butyric acid ethyl ester ((28g, 0.17 mol) {prepared following the method
described by Becher in J. Org. Chem, 64, pp.2814-2820, (1999)}) in ethanol (50 mL) was
heated to 90°C for 1 hour. The reaction mixture was concentrated, diluted with water and
ethyl acetate, then neutralized with HCl conc. The beige solid which precipitated out was
collected by filtration and dried under vacuum to yield **K1.1** (0.420g, 39%). ¹H-NMR
15 (DMSO-d₆) δ: 7.21 (4H, s), 6.94 (1H, s), 6.52 (2H, br, s), 5.36 (1H, s), 3.53 (2H, s), 2.45
(3H, s). HPLC: 100%, ret. time = 1.293 min., LC/MS (M+H)⁺ = 248.

K1.2: 2-[4-Chloro-6-(4-methylsulfanyl-benzyl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

20

**K1.2**

2-[4-(Carboxymethyl-carbamoyl)-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester



J3

5

To a solution of **J2** (0.100 g, 0.2 mmol) in DMF (3 mL) was added Glycine methyl ester hydrochloride (38 mg, 0.30 mmol), triethylamine (85 µL, 0.60 mmol) and benzothiazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (158 mg, 0.30 mmol). The mixture was stirred at 23°C for half an hour, then diluted with water and the precipitate was collected by filtration. The ester was saponified in ethanol (5 mL) and sodium hydroxide (0.5 mL) at 23°C in 1 hour. The mixture was then acidified with acetic acid, concentrated to remove ethanol and freeze dried. The resulting solid was triturated with water, filtered and vacuum dried to give pure **J3** (44 mg, 76%) as a white solid. ¹H-NMR (DMSO-d₆) δ: 11.84 (1H, br, s), 8.61 (1H, br, s), 8.22 (1H, br, s), 7.70 (2H, d, J=8Hz), 7.47 (2H, d, J=8Hz), 7.24 (2H, s), 6.80 (1H, s), 4.78 (2H, m), 4.15 (2H, q, J=7Hz), 3.71 (2H, br s), 2.43 (3H, merge with DMSO), 1.19 (3H, t, J=7 Hz). HPLC: 94.8%, ret. time = 1.330 min., LC/MS (M+H)⁺ = 550.

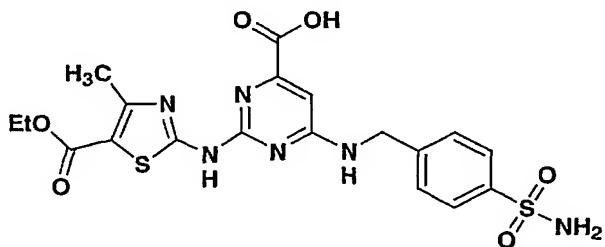
Example K1

20 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methylsulfanyl-benzyl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

A solution made of **J1.3** (0.719 g, 1.9 mmol), 4-aminomethylbenzenesulfonamide hydrochloride (0.520 g, 2.3 mmol) and triethylamine (530 μ L, 3.8 mmol) in N-methylpyrrolidinone (20 mL) was stirred at 90°C for 1 hour. The mixture was then cooled to room temperature, diluted with water and the white solid was collected by filtration to give pure **J1** (0.937 g, 95%). 1 H-NMR (DMSO-d₆) δ : 11.78 (1H, br, s), 8.58 (1H, br, s), 7.71 (2H, d, J=8Hz), 7.48 (2H, d, J=8Hz), 7.25 (2H, s), 6.80 (1H, s), 4.73 (2H, br,s), 4.26 (2H, q, J=7Hz), 4.15 (2H, q, J=7Hz), 2.43 (3H, merge with DMSO), 1.27 (3H, t, J=7Hz), 1.19 (3H, t, J=7Hz). HPLC: 91.3%, ret. time = 1.363 min., LC/MS (M+H)⁺ = 521.

Example J2

2-[4-Carboxyl-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazole carboxylic acid ethyl ester



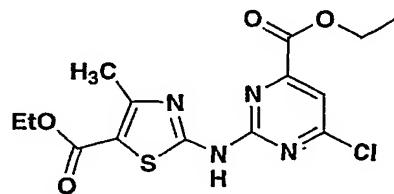
J2

15 A solution of **J1** (0.880 g, 1.7 mmol) in ethanol (10 mL) and sodium hydroxide (20%, 5 mL) was stirred at room temperature for 90 minutes. The mixture was then acidified with acetic acid to precipitate the salt, which is collected by filtration. The product is dissolved in DMF and purified by Prep HPLC (Acetonitrile/water/5mM 20 ammonium acetate, column Xterra C8 20x100 mm) to give **J2** (820 mg, 98%) as a white solid. $^1\text{H-NMR}$ (DMSO- d_6) δ : 13.33 (1H, br, s), 11.81 (1H, br, s), 8.63 (1H, br, s), 7.77 (2H, d, $J=8\text{Hz}$), 7.54 (2H, d, $J=8\text{Hz}$), 7.31 (2H, s), 6.84 (1H, s), 4.82 (2H, br,s), 4.22 (2H, q, $J=7\text{Hz}$), 2.49 (3H, merge with DMSO), 1.05 (3H, t, $J=7\text{Hz}$). HPLC: 96.9%, ret. time = 1.213 min., LC/MS ($\text{M}+\text{H})^+$ = 493.

Example J3

12.25 (1H, br s), 12.15 (1H, br s), 11.40 (1H, br, s), 5.72 (1H, s), 4.22 (2H, q, J=7Hz),
 4.12 (2H, q, J=7Hz), 1.27 (3H, t, J=7Hz), 1.22 (3H, t, J=7Hz). LC/MS^c: ret. time: 1.470
 min. (M+H)⁺: 315.

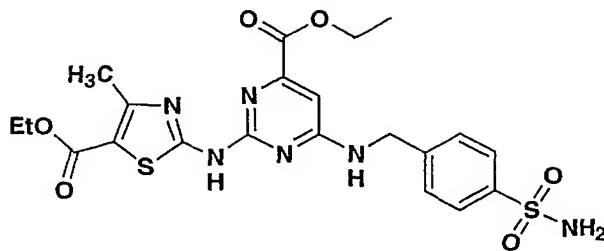
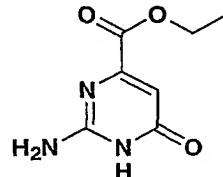
5 **J1.3 2-[[4-Ethoxycarbonyl-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazole carboxylic acid ethyl ester**



J1.3

10 **J1.2** (2.6 g, 8.27 mmol) was dissolved in aqueous sodium hydroxide (2N, 20 mL) and stirred at 90°C for 30 minutes. The mixture was then cooled in an ice-bath, acidified with concentrated hydrochloric acid and concentrated to dryness. The solid was suspended in an ethanolic hydrochloric acid solution (2M, 30 mL) and heated at 80°C for 2 hours. The mixture was concentrated, diluted with water and the white solid was collected by filtration. The thiourea and ethyl-2-chloroacetate (0.6 mL, 4.33 mmol) in ethanol (50mL) were stirred at reflux 24 hours, to give an insoluble product which after dilution with water, was collected by filtration and vacuum dried. The resulting solid was suspended in phosphorous oxychloride (30 mL) and stirred at 100°C for 2 hours. The mixture was then cooled to room temperature and added to ice/water and stirred for 2 hours. The beige solid which precipitated out was collected by filtration and dried under vacuum to yield **J1.3** (0.719 g, 23%). ¹H-NMR (DMSO-d₆) δ: 7.64 (1H, s), 4.40 (2H, q, J=7Hz), 4.25 (2H, q, J=7Hz), 2.55 (3H, s), 1.40 (3H, t, J=7Hz), 1.29 (3H, t, J=7Hz). LC/MS^c: ret. time: 1.980 min. (M+H)⁺: 371.

25 **J1.4 2-[[4-Ethoxycarbonyl-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazole carboxylic acid ethyl ester**

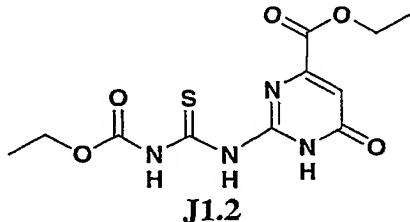
**J1****J1.1: 2-Amino-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester**

5

J1.1

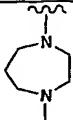
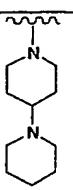
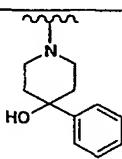
A solution of oxalacetic acid diethyl ester (8.5 g, 45.2 mmol) in ethanol (100 mL) was treated with guanidine carbonate (8.1 g, 45.2 mmol) and this was stirred under reflux for 2 hours. The mixture was diluted with water, concentrated to removed ethanol, and 10 the solid was collected by filtration. The solid was then suspended in ethanol (40 mL) and concentrated hydrochloric acid (1 mL) and refluxed for 15 minutes. The mixture was then cooled, basified with potassium carbonate, diluted with water and concentrated to removed ethanol. The white solid was collected by filtration and vacuum dried to give J1.1 (1.67 g, 20%). $^1\text{H-NMR}$ (DMSO- d_6) δ : 10.34 (1H, br s), 8.92 (1H, br s), 7.46 (1H, br, s), 5.42 (1H, s), 4.18 (2H, q, $J=7\text{Hz}$), 1.24 (3H, t, $J=7\text{Hz}$).

15
J1.2 4-(6-Oxo-2-ethoxycarbonylthiouido-1,6-dihydro-pyrimidin-4-yl)-carboxylic acid ethyl ester



20

A solution of J1.1 (1.67 g, 9.11 mmol) in dioxane (20 mL) was treated with ethoxycarbonyl isothiocyanate (1.07 mL, 9.11 mmol) and refluxed for 30 minutes. The mixture was then freeze dried to afford J1.2 (2.86 g, 100%). $^1\text{H-NMR}$ (DMSO- d_6) δ :

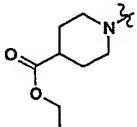
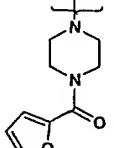
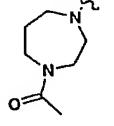
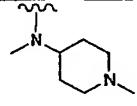
H16		2-[[4-[2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.127	100	603
H17	-N(CH ₂ CH ₂ OMe) ₂	2-[[4-[[Bis-(2-methoxy-ethyl)-carbamoyl]-methyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.293	87	622
H18		2-[[4-(2-[1,4]Bipiperidinyl-1'-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.153	100	657
H19		2-[[4-[2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.370	100	666

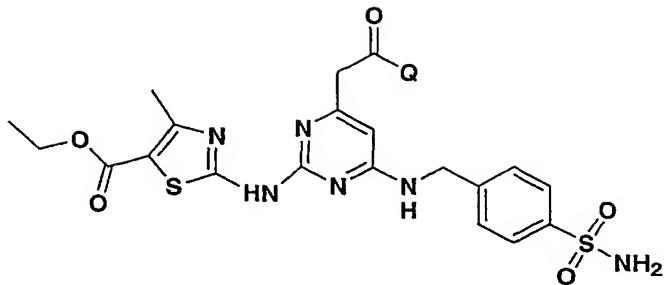
^aHPLC conditions used to determine retention times; 2 min gradient 0-100% B in A; (A; 0.05% TFA in 90/10 water/acetonitrile; B; 0.05%TFA in 10/90 water/acetonitrile) using a Primesphere C-18 4.6x30 mm column at 254 nm.

- 5 To avoid confusion in enumeration of the examples the letter "I" has been intentionally omitted. Thus there are no examples such as I1, etc. The example numbering proceeds directly from H#, to J#.

Example J1

- 10 2-[[4-Ethoxycarbonyl-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazole carboxylic acid ethyl ester

		ester			
H10		2-[4-[2-(4-Ethoxycarbonyl-piperidin-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.377	100	646
H11		2-[4-(2-oxo-2-piperidin-1-yl-ethyl)-6-(4-sulfamoyl-benzylamino) 2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.310	100	574
H12		2-[4-[2-[4-(Furan-2-carbonyl)-piperazin-1-yl]-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino) 2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.280	95	669
H13		2-[4-[(Cyclohexyl-methyl-carbamoyl)-methyl]-6-(4-sulfamoyl-benzylamino) 2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.460	89	601
H14		2-[4-[2-(4-Acetyl-[1,4]diazepan-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.207	100	631
H15		2-[4-[[Methyl-(1-methyl-piperidin-4-yl)-carbamoyl]-methyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.130	100	617

**Table H**

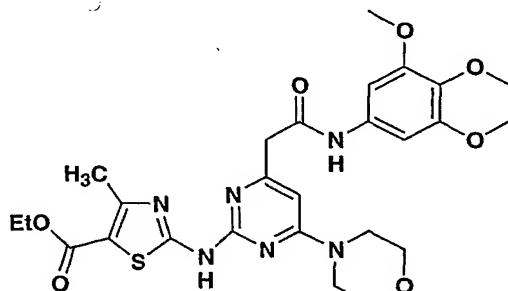
Ex.	Q	Name	HPLC Retention ^a (min)	% Purity	MS Reported (M+H) ⁺
H5		2-[[4-[2-oxo-2-(3-oxo-piperazin-1-yl)-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.163	100	589
H6		2-[[4-(4-sulfamoyl-benzylamino)-6-[(4-sulfamoyl-benzylcarbamoyl)-methyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.270	100	675
H7		2-[4-[2-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.277	91	632
H8		2-[[4-[[4-Chloro-phenyl]-methyl-carbamoyl]-methyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.483	100	630
H9		2-[[4-[2-(4-Hydroxy-piperidin-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.193	100	590

Primesphere C18 21x100 mm) to yield **H3** as a white solid (0.029 g, 86%). ¹H-NMR (DMSO-d₆) δ: 12.40 (1H, br, s), 11.50 (1H, br, s), 6.35 (1H, s), 4.09 (2H, q, J = 7 Hz), 3.58 (8H, m), 3.42 (2H, s), 2.39 (3H, s), 1.16 (3H, t, J = 7 Hz). HPLC: 95.2%, ret. time = 1.250 min., LC/MS (M+H)⁺ = 408.

5

Example H4

2-[4-Morpholin-4-yl-6-[(3,4,5-trimethoxy-phenylcarbamoyl)-methyl]-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester



10

H4

To a solution of **H3** (0.025 g, 0.061 mmol) in DMF was added 3,4,5-trimethoxyaniline (0.013 g, 0.073 mmol), a solution of containing
15 EDC/hydroxybenzotriazole in DMF (0.25M, 0.370 mL, 0.092 mmol) and N,N-diisopropylethylamine (32 μL, 0.183 mmol). Stirred at 23°C for 20 hrs. The mixture was then acidified with acetic acid (0.100 mL) and purified by Prep HPLC (Acetonitrile/water/5mM ammonium acetate, column Primesphere C18 21x100 mm) to yield **H4** as a white solid (0.024 g, 68%). ¹H-NMR (DMSO-d₆) δ: 11.58 (1H, br, s), 10.10 (1H, s), 6.98 (2H, s), 6.48 (1H, s), 4.15 (2H, q, J = 7 Hz), 3.66 (19H, m), 1.21 (3H, t, J = 7 Hz). HPLC: 93.0%, ret. time = 1.450 min., LC/MS (M+H)⁺ = 573.

Examples H5 to H19

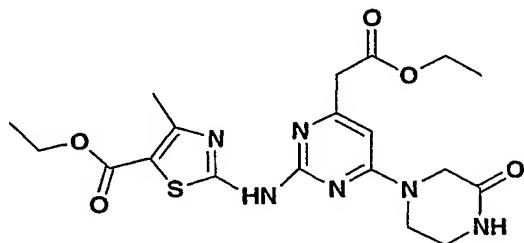
25 Examples **H2** to **H19** were prepared in a similar manner to that used for Example **H1** utilizing the appropriate amines.

pure **H1** as a white solid (0.249 g, 97%). $^1\text{H-NMR}$ (CDCl_3) δ : 6.20 (1H, s) 4.32 (2H, q, J = 7 Hz), 4.22 (2H, q, J = 7 Hz), 3.83 (4H, m), 3.73 (4H, br, s), 3.68 (2H, s), 2.66 (3H, s), 1.38 (3H, t, J = 7 Hz), 1.19 (3H, t, J = 7 Hz). HPLC: 96.2%, ret. time = 1.387 min., LC/MS ($M+\text{H}$) $^+$ = 436.

5

Example H2

2-[(4-Ethoxycarbonylmethyl-6-[3-oxo-1-piperazinyl]-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester



10

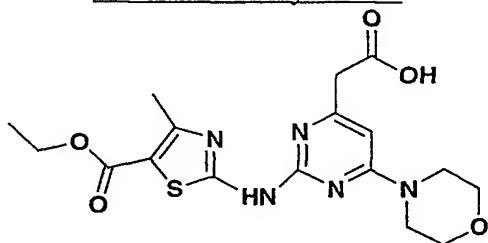
H2

Example **H2** was prepared in an analogous manner to example **H1** with the exception that morpholine was replaced by 2-piperazinone. HPLC: 95.7%, ret. time = 1.487 min., LC/MS ($M+\text{H}$) $^+$ = 449.

15

Example H3

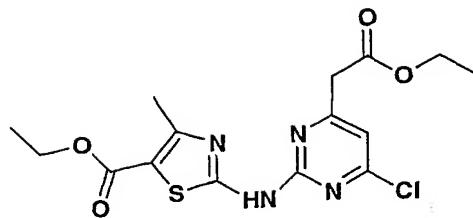
2-[(4-Carboxymethyl-6-morpholin-4-yl-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid

**H3**

20

H1.2 (0.036 g, 0.083 mmol) was added to a solution made of ethanol (5 mL) and sodium hydroxide (1N, 0.1 mL) and stirred at 23°C for 15 minutes. The mixture was then acidified to pH 4 with hydrogen chloride (1N), concentrated, dissolved in DMF and purified by Prep HPLC (Acetonitrile/water/5mM ammonium acetate, column

25

**H1.1**

5 **A1.1** (3.0 g, 13.14 mmol) was added to a solution of sodium ethoxide in ethanol (705 mg of sodium, 30 mmol in 100 mL of ethanol). The reaction mixture was heated in an oil bath at 100°C for 30 minutes during which time most, but not all, of the material had dissolved, and diethyl-3-oxoglutarate (4.00 g, 19.74 mmol) was added dropwise over 30 minutes. The reaction mixture was maintained in an oil bath to 100°C for 16 hours.

10 An additional 2.4 mL of diethyl-3-oxoglutarate were added and the reaction mixture refluxed for an additional 4 hours after which HPLC analysis indicated only a trace amount of starting material remained. The reaction mixture was allowed to cool to room temperature, added to 300 mL of ice/10% sulfuric acid, stirred 30 minutes and the solid was collected by filtration and dried to give a brown solid.

15 The residue was dissolved in phosphorous oxychloride (15 mL) and stirred at 55°C for 3 hours. The mixture was then added to ice/water. After the ice melted the solid was collected by filtration and, dried under vacuum and purified by flash chromatography (Hexane/ethyl acetate 30% to 100%) to yield **H1.1** as a light yellow foam (1.63 g, 32%).

16 $^1\text{H-NMR}$ (CDCl_3) δ : 7.02 (1H, s), 4.37 (2H, q, $J = 7$ Hz), 4.28 (2H, q, $J = 7$ Hz), 3.83 (2H, s), 2.74 (3H, s), 1.42 (3H, t, $J = 7$ Hz), 1.33 (3H, t, $J = 7$ Hz). HPLC: 96.4%, ret. time = 1.990 min., LC/MS ($M+\text{H}^+$) = 385.

H1.2 2-[4-(4-Ethoxycarbonylmethyl-6-morpholin-4-yl-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

25 A mixture of **H1.1** (0.229 g, 0.59 mmol) and morpholine (0.100 mL, 1.18 mmol) in tetrahydrofuran was stirred at 50°C for 2.5 hours. The mixture was then concentrated, and purified by flash chromatographiy (Dichloromethane/Methanol 2% to 10%) to give

G15			-OMe	2-[[4-[N-[3,4,5-(Trimethoxy)phenyl]methyl]-N-methylamino]-5-methoxy-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.65 ^b	602.18
G16				2-[[4-[[3-pyridyl]methoxy]-5-(2-propenyl)-6-(4-morpholinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	3.29	497.07

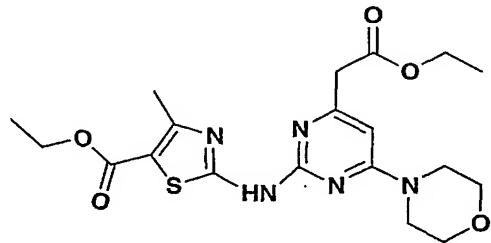
^aHPLC conditions used to determine retention times; 4 min gradient 0-100% B in A(A; 0.1% TFA in 90/10 water/methanol; B; 0.1%TFA in 10/90 water/methanol) using a YMC turbopack column at 254 nm. ^bYMC ODS 5 μ m C18 column 4.6 x 30 mm (2 min)

^cWaters Xterra 4.6 x 30 5 μ C18, 4 min gradient, 0-100% B in A(A; 0.2% H₃PO₄ in 90/10 water/methanol; B; 0.2%H₃PO₄ in 10/90 water/methanol) at 220 nm

Example H1

2-[(4-Ethoxycarbonylmethyl-6-morpholin-4-yl-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

10



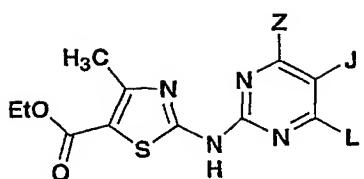
H1

H1.1 2-[(4-Chloro-6-ethoxycarbonylmethyl-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

15

				methyl-5-thiazolecarboxylic acid, ethyl ester		
G10			-CH ₃	2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-5-methyl-6-(4-tert-butyloxycarbonyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	3.60	647.32
G11			-CH ₃	2-[[4-[N-[[3,4,5-(Trimethoxy)phenyl]methyl]N-methylamino]-5-methyl-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.64 ^b	586.34
G12			-CH ₃	2-[4,6-Bis-(4-hydroxy-1-piperidin-1-yl)-5-methylpyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.55 ^b	477.20
G13				2-[4,6-Bis-(3-oxo-piperazin-1-yl)-5-[ethoxycarbonylmethyl]pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	2.89	547.29
G14			-OMe	2-[4,6-Bis-(4-hydroxy-1-piperidin-1-yl)-5-methoxypyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.62 ^b	493.21

G5				2-[[4-[[5-[2-[2-Methylprop-3-enyl]amino]-6-(4-methylpiperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.93	615.50
G6			-CH ₃	2-[[4-[[3,4,5-(Trimethoxy)phenyl]methyl]amino]-5-methyl-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate	1.64 ^b	572.26
G7				2-[[4-[[5-[2,3-propandiol][4-(aminosulfonyl)phenyl]methyl]amino]-6-(4-methylpiperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.29	621.50
G8			-CH ₃	2-[[4-[[3,4,5-(Trimethoxy)phenyl]methyl]amino]-5-methyl-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate	1.35 ^c	572.31
G9		-Cl		2-[[4-[[5-[2-[2-Methylprop-3-enyl]amino]-6-(4-methylpiperazinyl)-2-pyrimidinyl]amino]-4-chloro-2-pyrimidinyl]amino]-4-	3.47	551.35



Examples G2 to G16 were prepared in a similar manner to that used for Example G1 utilizing the appropriate replacement for diethyl allylmalonate in step G1.1.

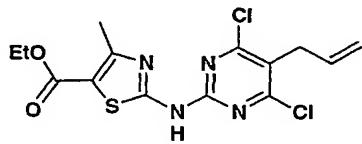
5

Table G

Ex.	Z	L	J	Name	HPLC Retention ^a (min)	MS Reported
G2			-CH ₃	2-[4-[[4-(Aminosulfonyl)phenyl]methyl]amino]-5-methyl-6-(1-piperazinyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:3)	2.31	547.23
G3			-CH ₃	2-[4-[[4-(Aminosulfonyl)phenyl]methyl]amino]-5-methyl-6-(4-morpholinyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester.	2.84	548.22
G4				2-[4-[[5-Allyl[4-(aminosulfonyl)phenyl]methyl]amino]-6-(4-methylpiperazinyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	2.47	587.51

homogeneous. **A1.1** (350 mg, 1.53 mmol) was then added and the mixture was stirred for 20 min. Diethyl allylmalonate (0.30 mL, 1.53 mmol) was added dropwise, the reaction mixture was heated at reflux for 22 hr, and then cooled and poured onto a mixture of 10% aqueous H₂SO₄ and ice. The solid was collected by filtration, washed with water and dried to afford 346 mg (67% yield) of **G1.1** as a tan solid. LC/MS: 337.58 [M+H]⁺

5 **G1.2: 2-[(5-Allyl-4,6-dichloropyrimidin-2-yl)amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester**



10 **G1.2**

10 A mixture of **G1.1** (346 mg, 1.03 mmol) and POCl₃ (5 mL) was heated at 100 °C for 19 hr. The reaction mixture was poured slowly onto a mixture of ethyl acetate, 2 N NaOH and ice. The layers were separated and the organic phase was washed with sat. NaHCO₃, water and brine, dried over MgSO₄ and concentrated. Afforded 285 mg (74% yield) of **G1.2** as a yellow solid. LC/MS: 373.49 [M+H]⁺; ¹H NMR (400 MHz, d₆-DMSO): δ 5.90 (m, 1 H), 5.10 (m, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 3.51 (m, 2 H), 2.55 (s, 3 H), 1.29 (t, J = 7.1 Hz, 3 H).

20 **G1.3: 2-[[4-[5-Allyl[4-(aminosulfonyl)phenyl]methyl]amino]-6-chloro-2-pyrimidinyllamino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester**

25 A mixture of **G1.2** (51 mg, 0.137 mmol), 4-aminomethylbenzenesulfonamide hydrochloride (32 mg, 0.143 mmol), (iPr)₂NEt (70 μL, 0.411 mmol) and iPrOH (0.6 mL) was heated at 105 °C in a sealed tube for 24 hr. The reaction mixture was cooled to room temperature and the precipitated solid was collected by filtration and washed with water, iPrOH, and ether. Afforded 63 mg (88% yield) of **G1** as a tan solid: LC/MS: 523.49 [M+H]⁺

Example G2-G16

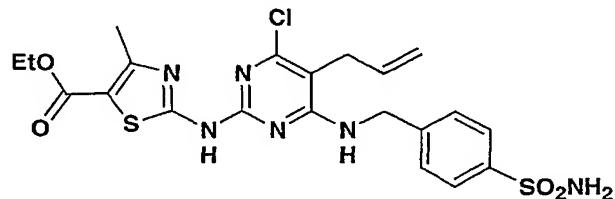
F8		2-[4-(4-Acetyl-[1,4]diazepan-1-yl)-6-(4-carboxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.32	525.34
F9		2-{4-(4-Carboxy-phenyl)-6-[N-methyl-N-(1-N-methyl-piperidin-4-yl)-amino]-pyrimidin-2-ylamino}-4-methylthiazole-5-carboxylic acid ethyl ester	1.17	511.37
F10		2-[4-(4-Carboxy-phenyl)-6-piperazin-1-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.19	469.34
F11		2-[4-(4-Carboxy-phenyl)-6-(4-sulfamoyl-benzylamino)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.36	569.26

^aHPLC conditions used to determine retention times: 2 min gradient 0-100%B in A(A; 0.05% TFA in 90/10 water/acetonitrile; B; 0.05%TFA in 10/90 water/acetonitrile) using a Primesphere C18 4.6 x 30 mm column at 220 nm.

5

Example G1

2-[(4-[[5-Allyl[4-(aminosulfonyl)phenyl]methyl]amino]-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester



G1

10 G1.1: 2-[(5-Allyl-4,6-(1H,5H)pyrimidinedion-2yl)amino-4-methyl-5-thiazolecarboxylic acid ethyl ester



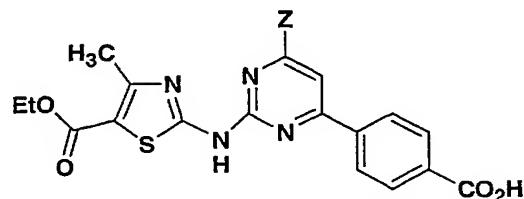
G1.1

15 A solution of NaOEt in EtOH was prepared by stirring Na (88 mg, 3.83 mmol) with absolute EtOH (15 mL) at room temperature until the mixture became

4.22 (2H, m), 1.38 (1H, m), 3.42 (2H, m), 2.52 (3H, s), 1.83 (2H, m), 1.41 (2H, m), 1.29 (3H, t, $J = 7.1$ Hz); HPLC: 100%; ret. time^c = 1.32 min.; LC/MS ($M+H$)⁺ = 484.

Example F2-F11

5

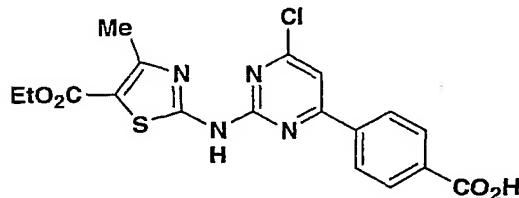


Examples F2 to F11 were prepared in a similar manner to that used for Example F1 utilizing the appropriate amines.

Table F

Ex.	Z	Name	HPLC Retention ^a (min)	MS Reported
F2		2-[4-(4-Carboxy-phenyl)-6-(3-oxo-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.25	483.31
F3		2-[4-(4-Carboxy-phenyl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.21	483.37
F4		2-[4-(4-Carboxy-phenyl)-6-morpholin-4-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.28	470.05
F5		2-[4-(4-Carboxy-phenyl)-6-(4-methyl-[1,4]diazepan-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.17	497.34
F6		2-[4-(4-Carboxy-phenyl)-6-(3-R-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.37	484.35
F7		2-[4-(4-Carboxy-phenyl)-6-(3-hydroxymethyl-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.40	498.32

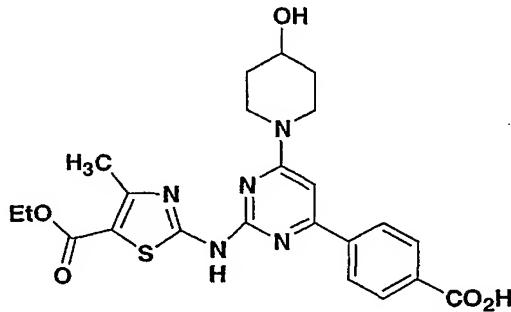
F1.5: 2-[4-(4-Carboxy-phenyl)-6-chloro-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester

**F1.5**

A solution of **F1.4** (980 mg, 3.2 mmol) and ethyl 2 chloroacetoacetate (630 mg, 3.84 mmol) in EtOH (45 mL) was heated at 100°C for 16 hours. The reaction was cooled and the resulting precipitate was collected by filtration to afford **F1.5** (570 mg, 43%). ¹H-NMR (DMSO-d₆) δ: 8.42 (2H, d, *J* = 8.4 Hz), 8.11 (2H, d, *J* = 8.3 Hz), 7.95 (1H, s), 4.26 (2H, q, *J* = 7.1 Hz), 1.31 (3H, t, *J* = 7.1 Hz); HPLC: 95%; ret. time^b = 1.87 min.; LC/MS (M+H)⁺ = 419.

F1.6 2-[4-(4-Carboxy-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester

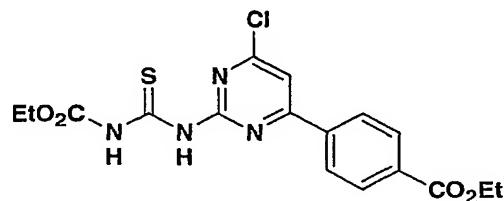
15

**F1**

A solution of **F1.5** (21 mg, 50 μmol), 4-hydroxypiperidine (200 μL, 0.5M in DMF, 100 μmol) and Et₃N (20 μL) in DMF (1.5 mL) was heated to 80°C for 4 hours. The reaction 20 was diluted to 2 mL with DMF, filtered then the filtrate subjected to purification by preparative HPLC to obtained **F1** (5.7 mg, 24%). ¹H-NMR (DMSO-d₆) δ: 8.31 (2H, d, *J* = 8.3 Hz), 8.03 (2H, d, *J* = 8.3 Hz), 7.10 (1H, s), 4.80 (1H, bs), 4.22 (2H, q, *J* = 7.1 Hz),

DMSO-d₆) δ: 8.22 (2H, d, *J* = 8.6 Hz), 8.06 (2H, d, *J* = 8.6 Hz), 7.32 (1H, s), 7.26 (2H, bs), 4.34 (2H, q, *J* = 7.1 Hz), 1.33 (3H, t, *J* = 7.1 Hz); HPLC: 92%; ret. time^b = 1.87 min.; LC/MS (M+H)⁺ = 278.

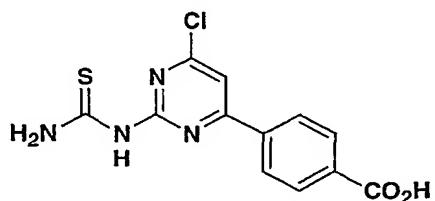
5 **F1.3:** 4-(6-Chloro-2-ethoxycarbonylthioureido-pyrimidin-4-yl)-benzoic acid ethyl ester



F1.3

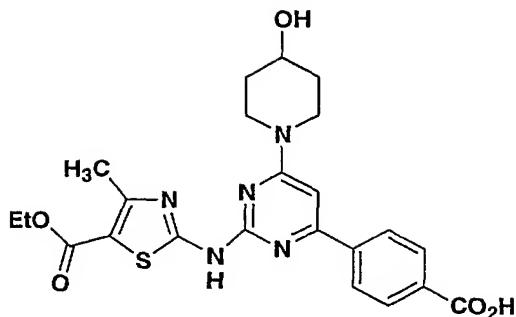
A solution of **F1.2** (1.18 g, 4.26 mmol) and ethoxycarbonylisothiocyanate (1.12 g, 8.52 mmol) in dioxane (40 mL) was heated at 100°C for 16 hours. The reaction was cooled to rt and Et₂O and hexane were added. The resulting precipitate was collected by filtration to afford **F1.3** (1.36 g, 78%). ¹H-NMR (DMSO-d₆) δ: 12.43 (1H, s), 12.08 (1H, s), 8.37 (2H, d, *J* = 8.6 Hz), 8.13 (1H, s), 8.10 (2H, d, *J* = 8.6 Hz), 4.36 (2H, q, *J* = 7.1 Hz), 4.18 (2H, q, *J* = 7.1 Hz), 1.34 (3H, t, *J* = 7.1 Hz), 1.24 (3H, t, *J* = 7.1 Hz); HPLC: 95%; ret. time^b = 2.15 min.; LC/MS (M+H)⁺ = 409.

10 **F1.4:** 4-(6-Chloro-2-thioureido-pyrimidin-4-yl)-benzoic acid

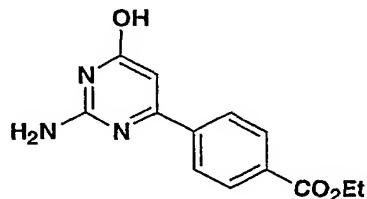


F1.4

20 A solution of **F1.3** (1.3 g, 3.2 mmol) in 2N NaOH (25 mL) was stirred at rt for 2 hours. The reaction was acidified with 2N HCl. The resulting precipitate was collected by filtration to obtain **F1.4** (982 mg, 100%). ¹H-NMR (DMSO-d₆) δ: 11.07 (1H, s), 9.93 (1H, d, *J* = 3.0 Hz), 9.38 (1H, s), 8.31 (2H, d, *J* = 8.5 Hz), 8.15 (2H, d, *J* = 8.5 Hz), 8.14 (1H, s); HPLC: 95%; ret. time^b = 1.05 min.; LC/MS (M-H)⁻ = 307.

**F1**

F1.1: 4-(2-Amino-6-hydroxy-pyrimidin-4-yl)-benzoic acid ethyl ester



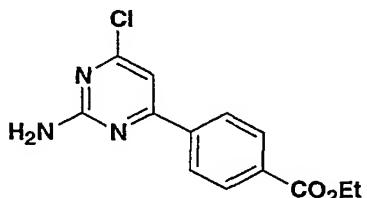
5

F1.1

A solution of 4-methoxycarbonylbenzoylacetic acid methyl ester (5.0 g, 21.2 mmol) and guanidine carbonate (3.82 g, 21.2 mmol) in ethanol (150 mL) was heated at reflux for 4 hours. The reaction was cooled to rt then 2N HCl (40 mL) was added. The resulting solid was collected by filtration to afford **F1.1** (7.1 g) as a carbonate salt which was used as is in the subsequent step. HPLC: 90%; ret. time^b = 1.30 min.; LC/MS ($M+H$)⁺ = 261.

10

F1.2: 4-(2-Amino-6-chloro-pyrimidin-4-yl)-benzoic acid ethyl ester



15

F1.2

A solution of **F1.1** (4.0 g, 12.5 mmol) in POCl_3 (15 mL) was heated at 100°C for 4 hours. The reaction was cooled to RT, partitioned between EtOAc and NaHCO_3 , the organic phase was dried (MgSO_4), filtered and concentrated. The residue was purified by flash chromatography (10%→100% EtOAc/hexane) to afford **F1.2** (1.183 g). $^1\text{H-NMR}$ (

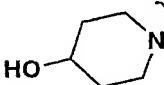
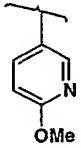
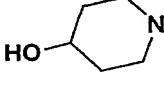
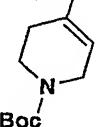
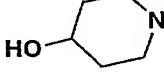
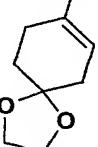
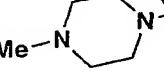
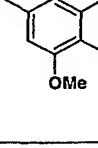
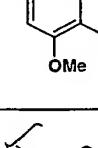
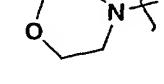
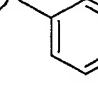
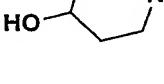
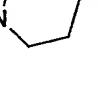
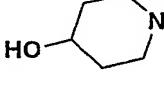
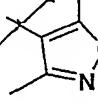
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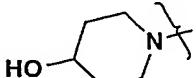
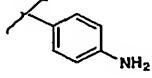
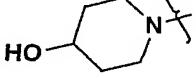
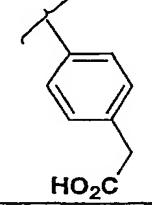
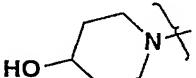
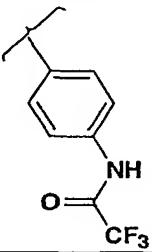
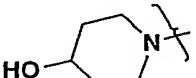
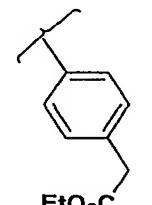
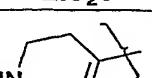
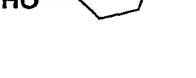
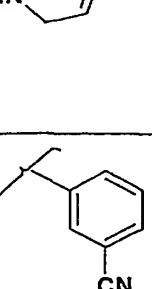
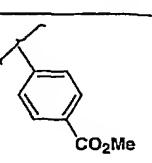
E27			2-[4-(4-tert-Butoxycarbonylaminophenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.87	555
E28			2-[4-(4-Cyano-phenyl)-6-(4-methanesulfonylbenzylamino)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.79	549
E29			2-[4-(4-Methanesulfonylphenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.35	518
E30			2-[4-(4-Methanesulfanylphenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.65	486

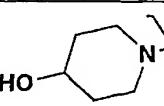
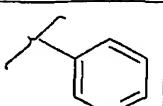
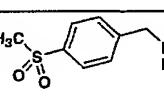
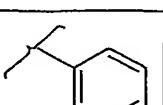
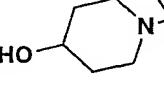
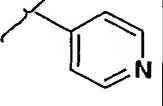
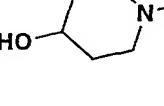
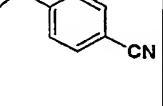
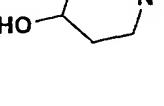
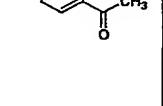
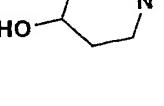
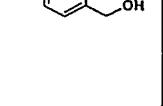
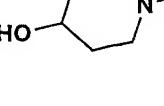
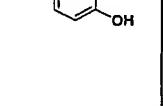
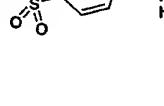
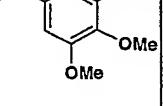
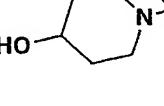
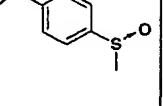
^aHPLC conditions used to determine retention times: 2 min gradient 0-100% B in A(A; 0.05% TFA in 90/10 water/acetonitrile; B; 0.05%TFA in 10/90 water/acetonitrile) using a Primesphere C4 4.6 x 30 mm column at 254 nm. ^b2 min gradient 0-100% B in A(A; 5mM NH₄OAc in 90/10 water/acetonitrile; B; 5mM NH₄OAc in 10/90 water/acetonitrile) using a Primesphere C4 4.6 x 30 mm column at 254 nm.

Example F1

2-[4-(4-Carboxy-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester

			acid ethyl ester		
E19			2-[4-(2-(Methoxy)-5-pyridinyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.66	471
E20			2-[4-(4-tertButyloxycarbonyl-1,2,3,6-Tetrahydropyridin-4-yl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.83	545
E21			2-[4-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.27	502
E22			2-[4-(4-Methyl-1-piperazinyl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	2.20	528
E23			2-[4-(4-Morpholinyl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	2.04	515
E24			2-[4-(4-Morpholinyl)-6-(3-pyridinyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.29	427
E25			2-[4-(Piperadin-4-yl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.23	447
E26			2-[[4-[4-Hydroxy-piperidinyl]-6-(3,5-dimethyl-4-isoxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.31	459

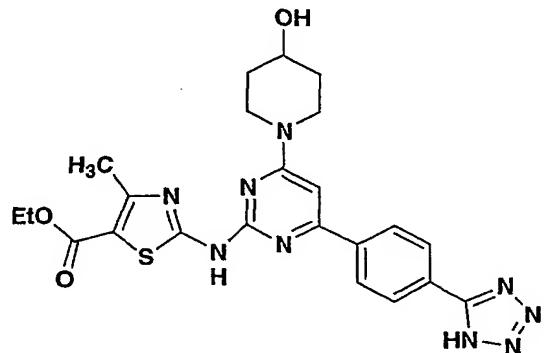
			methylthiazole-5-carboxylic acid ethyl ester		
E12			2-[4-(4-(Amino)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.54	455
E13			2-[4-(4-Carboxymethyl-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.31	498
E14			2-[4-(4-(Trifluoromethylcarbonylamino)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.50	551
E15			2-[4-(4-(Ethoxycarbonylmethyl)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.50	526
E16			2-[4-(1,2,3,6-Tetrahydropyridin-4-yl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.16	445
E17			2-[4-(3-(cyano)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.43	465
E18			2-[4-(4-(Methoxycarbonyl)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.73	498

Ex.	Z	L	Name	HPLC Retention ^a (min)	MS Reported
E3			2-[4-(4-Hydroxy-piperidin-1-yl)-6-pyridin-3-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.21	441
E4			2-[4-(4-Methanesulfonyl-benzylamino)-6-pyridin-3-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.54 ^b	525
E5			2-[4-(4-Hydroxy-piperidin-1-yl)-6-pyridin-4-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.14	441
E6			2-[4-(4-Cyano-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.43	465
E7			2-[4-(4-Acetyl-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.37	482
E8			2-[4-(4-Hydroxymethyl-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.29	470
E9			2-[4-(4-Hydroxy-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.32	456
E10			2-[4-(4-Methanesulfonyl-benzylamino)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester	1.51	614
E11			2-[4-(4-Methanesulfinylphenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-	1.26	502

Example E2

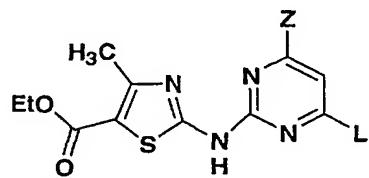
2-[4-(4-Hydroxy-piperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester

5



E2

A solution of E6 (52 mg, 0.1119 mmol), sodium azide (92 mg, 1.415 mmol) and ammonium chloride (85 mg, 1.586 mmol) in DMF (2 mL) in a quartz microwave reactor 10 was irradiated for 15 min at 300W so as to maintain a reactive temperature of 175°C. Upon cooling, the reaction was filtered and purified by preparative HPLC to afford E2 (25 mg, 44%). ¹H-NMR (DMSO-d₆) δ: 11.66 (1H, bs), 8.41 (2H, d, *J* = 8.2 Hz), 8.15 (2H, d, *J* = 8.2 Hz), 7.13 (1H, s), 4.81 (1H, bs), 4.23 (2H, q, *J* = 7.1 Hz), 4.22 (2H, m), 3.81 (1H, bs), 3.43 (2H, m), 2.53 (3H, s), 1.84 (2H, m), 1.40 (2H, m), 1.30 (3H, t, *J* = 7.1 Hz); HPLC: 100%, ret. time^a = 1.30 min., LC/MS (M+H)⁺ = 508.

Example E3-E30

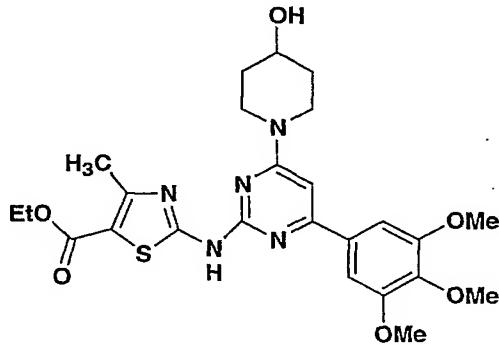
20 Examples E3 to E30 were prepared in a similar manner to that used for Example E1 utilizing the appropriate amines and organometallic coupling partner.

Table E

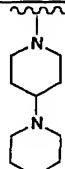
E1.1

A suspension solution of **A1.3** (6.04 g, 18.1 mmol), 4-hydroxypiperidine (1.84 g, 18.2 mmol) and diisopropylethylamine (6.3 ml, 36.2 mmol) in ethanol (30 mL) was heated to 50°C for 16 hours. After cooling to room temperature, the precipitated solid was collected by filtration and washed with ethanol to yield **E1.1** (4.72 g, 65%). ¹H-NMR (DMSO-d₆) δ: 11.82 (1H, bs), 6.59 (1H, s), 4.82 (1H, d, *J* = 4.0 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 3.79 (1H, m), 3.40 (2H, m), 2.50 (3H, s), 1.80 (2H, m), 1.40 (2H, m), 1.26 (3H, t, *J* = 7.1 Hz); HPLC: 95%, ret. time^a = 1.50 min., LC/MS (M+H)⁺ = 398.

E1.2 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester

**E1.2**

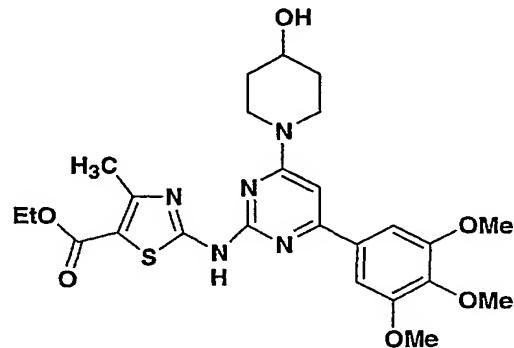
A solution of **E1.1** (147 mg, 0.370 mmol), 3,4,5-trimethoxyphenylboronic acid (130 mg, 0.613 mmol), Pd(PPh₃)₄ (21 mg, 0.018 mmol) and K₂CO₃ (2mL of 2M aqueous solution) in 1,2-dimethoxyethane (10 mL) and ethanol (3 mL) under argon atmosphere was heated at reflux for 16 h. The reaction was concentrated, the residue dissolved in DMF, filtered through cotton and a plug C-18 silica gel. The resulting solution was directly purified on the preparative HPLC. Fractions containing the product were slightly concentrated and the resulting precipitate collected by filtration, washed with water, to afford **E1** (89 mg, 45%) as a light pink solid. ¹H-NMR (DMSO-d₆) δ: 11.55 (1H, s), 7.58 (2H, s), 7.02 (1H, s), 4.80 (1H, d, *J* = 4.0 Hz), 4.22 (2H, q, *J* = 7.1 Hz), 4.22 (2H, m), 3.93 (6H, s), 3.77 (1H, m), 3.72 (3H, s), 3.36 (2H, m), 2.52 (3H, s), 1.80 (2H, m), 1.40 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz); HPLC: 95%, ret. time^a = 1.44 min., LC/MS (M+H)⁺ = 530.

		5-thiazolecarboxylic acid ethyl ester			
D17		2-[[4-[(1',4)-Bipiperidinyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.13	99	498.38

^aHPLC conditions used to determine retention times; 2 min gradient 0-100% B in A; (A; 0.05% TFA in 90/10 water/acetonitrile; B; 0.05%TFA in 10/90 water/acetonitrile) using a X-terra C-8 4.6x30 mm column at 254 nm

Example E1

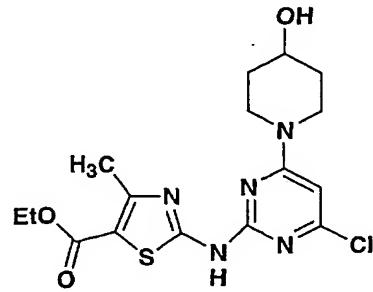
- 5 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester

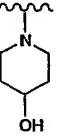
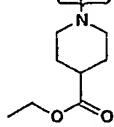
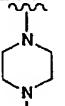
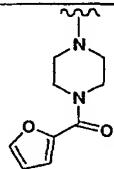
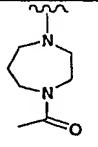
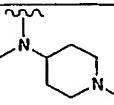
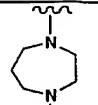


E1

10

- E1.1 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester



D8		2-[[4-[4-Hydroxy-piperidinyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.19	100	431.35
D9		2-[[4-[4-Ethoxycarbonyl-piperidinyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.47	94	487.35
D10		2-[[4-Piperidinyl-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.42	97	415.36
D11		2-[[4-[N-Methylpiperazinyl-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.11	94	430.37
D12		2-[[4-[N-(2-Furylcarbonyl)piperazinyl-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.35	91	510.33
D13		2-[[4-[N-Acetyl-[1,4]-diazepyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.2	100	472.34
D14		2-[[4-[N-Methyl-N-(N-methyl-4-piperidinyl)-amino]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.07	93	458.37
D15		2-[[4-[N-Methyl-[1,4]-diazepyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.07	100	444.34
D16	-N(CH ₂ CH ₂ OMe) ₂	2-[[4-N,N-Dimethoxyethylamino]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-	1.34	96	463.4

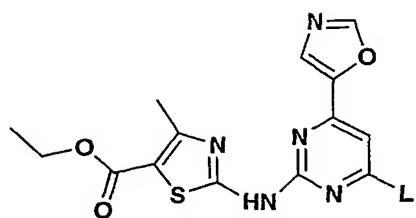
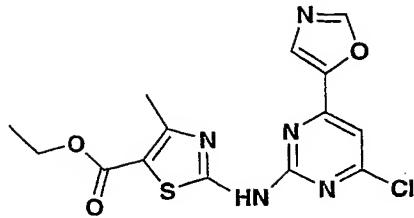


Table D

Ex.	L	Name	HPLC Retention ^a (min)	% Purity	MS Reported
D2		2-[[4-[(4-Aminosulfonylphenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.28	95	516.33
D3		2-[[4-Morpholino-6-(5-oxazolyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.3	100	417.32
D4		2-[[4-[(3,4-Dimethoxyphenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.39	89	497.34
D5		2-[[4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-6-(5-oxazolyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.37	100	473.39
D6		2-[[4-[4-Hydroxy-4-phenylpiperidinyl]-6-(5-oxazolyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.47	89	507.39
D7		2-[[4-[(4-Methylsulfonylphenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester	1.32	97	515.29



A mixture of **D1.4** (0.515 g, 1.57 mmol), TOSMIC (0.307 g, 1.57 mmol) and potassium carbonate (0.217 g, 1.57 mmol) in ethanol (30 mL) was refluxed for 2 hours. The mixture was then cooled to room temperature and diluted with water. The precipitated solid was collected by filtration and dried under vacuum to provide **D1.5** (0.482 g, 75%).
 5 $^1\text{H-NMR}$ (DMSO-d₆) δ : 12.68 (1H, br s), 8.82 (1H, s), 8.15 (1H, s), 7.66 (1H, s), 4.29 (2H, q, *J*=7.1 Hz), 2.56 (3H, s), 1.34 (3H, t, *J*=7.2 Hz). LC/MS^c: ret. time: 1.807 min.
 (M+H)⁺: 366.28.

10 **D1.6** 2-[4-[(4-Chlorophenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

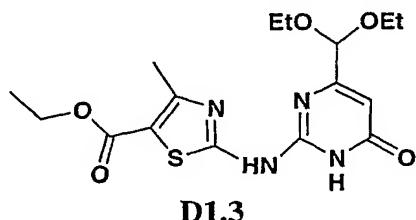
A mixture of **D1.5** (0.048 g, 0.131 mmol) and 4-chlorobenzylamine (0.032 mL, 0.262 mmol) in N-methylpyrrolidinone was stirred at 60°C for 2 hours. The mixture was then concentrated, dissolved in DMF and purified by Prep HPLC (Acetonitrile/water/0.1%TFA, column Xterra C8 20x100 mm). The residue was then triturated in methanol to yield **D1** (0.049 g, 65%) as a beige solid. $^1\text{H-NMR}$ (DMSO-d₆) δ : 11.72 (1H, br s), 8.56 (1H, s), 8.39 (1H, br s), 7.66 (1H, s), 7.36 (4H, m), 6.51 (1H, s), 4.68 (2H, br s), 4.18 (2H, q, *J*=7.1 Hz), 1.22 (3H, t, *J*=7.1 Hz). LC/MS^c: ret. time: 1.703 min. (M+H)⁺: 471.30.

Examples D2 to D17

Examples **D2** to **D17** were prepared in a similar manner to that used for Example **D1** utilizing the appropriate amines and N,N-dimethylformamide as the solvent instead of N-methylpyrrolidinone.

D1.3 2-[(4-Diethoxymethyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

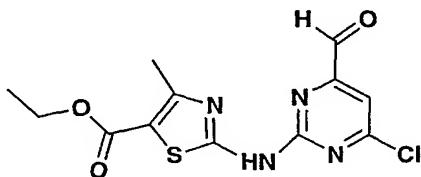
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A mixture of **D1.2** (3.62 g, 13.29 mmol) and ethyl 2-chloroacetate (1.86 mL, 13.29 mmol) in ethanol (250 mL) was refluxed for 20 hours. The mixture was then diluted with water and the solid collected by filtration to afford **D1.3** (3.9 g, 76%). ¹H-NMR (DMSO-d₆) δ: 11.84 (2H, br s), 5.24 (1H, br s), 4.23 (2H, q, J=7.1 Hz), 3.64 (4H, m), 1.27 (3H, t, J=7.2 Hz), 1.20 (6H, t, J = 7.0 Hz). LC/MS^c: ret. time: 1.663 min. (M+H)⁺: 383.

D1.4 2-[(4-Formyl-6-chloro-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

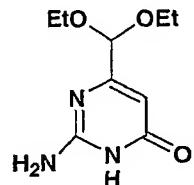
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A solution of **D1.3** (0.500 g, 1.31 mmol) in phosphorous oxychloride (5 mL) was stirred at 60°C for 2 hours. The mixture was then added to ice/water and stirred for 30 minutes. Saturated sodium carbonate was then added and this was diluted with ethyl acetate/tetrahydrofuran. The aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to give **D1.4** (0.330 g, 77%). ¹H-NMR (DMSO-d₆) δ: 11.92 (1H, br s), 9.95 (1H, s), 7.66 (1H, s), 4.33 (2H, q, J=7.1 Hz), 2.63 (3H, s), 1.36 (3H, t, J=7.1 Hz). LC/MS^c: 86.1%, ret. time: 1.413 min. (M+H₂O+H)⁺: 345.33.

25

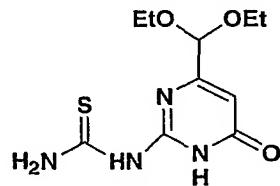
D1.5 2-[(4-Oxazol-5-yl-6-chloro-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester

D1**D1.1: 2-Amino-6-diethoxymethyl-3H-pyrimidin-4-one****D1.1**

- 5 A solution of 4,4-diethoxy-3-oxo-butyric acid ethyl ester [Johnson, T.B. and Mikeska, L.A. J. Am. Chem. Soc. **41**, 810 (1919)] (18.0 g, 82.5 mol) in ethanol (300 mL) was treated with guanidine carbonate (14.8 g, 82.5 mol) and this was stirred under reflux until no solid remained (~ 4 hours). The mixture was concentrated, diluted with water and the solid was collected by filtration to give **D1.1** (13.1 g, 74%) as a beige solid. ¹H-NMR (DMSO-d₆) δ: 10.78 (1H, br s), 6.61 (2H, br s), 5.63 (1H, s), 4.90 (1H, s), 3.51 (4H, m), 1.13 (6H, t, *J*=7.1 Hz). LC/MS^c: ret. time: 0.757 min. (M+H)⁺: 214. M.p.: 198.0-202.7°C.

D1.2 (4-Diethoxymethyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)- thiourea

15

**D1.2**

- A solution of **D1.1** (1.0 g, 4.69 mmol) in dioxane (18 mL) was treated with ethoxycarbonyl isothiocyanate (0.553 mL, 4.69 mmol) and refluxed for 30 minutes. The mixture was then freeze dried to afford the crude (4-diethoxymethyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-(ethoxycarbonyl)-thiourea (1.6 g, 100%). LC/MS^c: ret. time: 1.527 min. (M+H)⁺: 345.40.

- The residue was dissolved in sodium hydroxide (2N, 50 mL) and stirred at 100°C for 30 minutes. The mixture was then cooled in an ice-bath and acidified with concentrated hydrochloric acid. The solid was collected by filtration and dried under vacuum to give **D1.2** (0.740 g, 59%). HPLC^b: 96.6%, ret. time: 0.844 min.

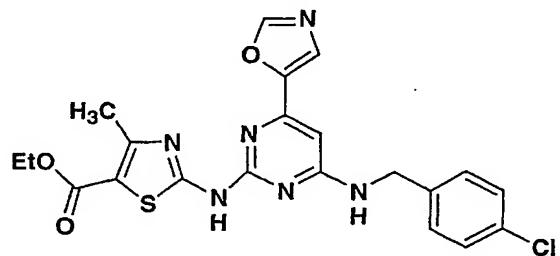
		yl-thiazole-5-carboxylic acid ethyl ester		
C9		2-{4-(3-Hydroxy-1-pyrrolidinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.59	522.59
C10		4-Methyl-2-{{[2-[4-morpholin-4-yl]ethyl]amino}-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-thiazole-5-carboxylic acid ethyl ester	1.42	579.69
C11		4-Methyl-2-{{[4-hydroxy]butyl]amino}-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-thiazole-5-carboxylic acid ethyl ester	1.507	524.61
C12		2-{4-(4-Formyl-1-piperazinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.46	549.62

^aHPLC conditions used to determine retention times; 4 min gradient 0-100% B in A(A; 0.1% TFA in 90/10 water/methanol; B; 0.1%TFA in 10/90 water/methanol) using a YMC turbopack column at 254 nm. * Waters Xterra 4.6x30 5u C18 (2min) Solvent A and B as above.

5

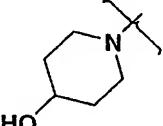
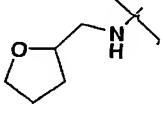
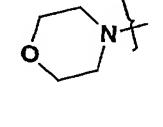
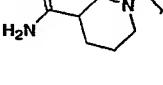
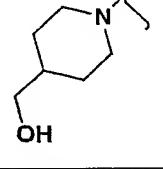
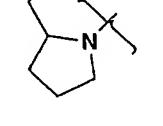
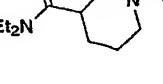
Example D1

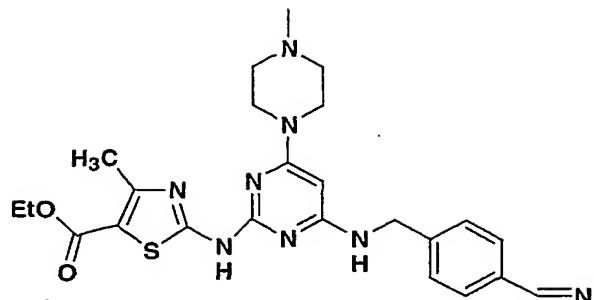
2-{{[4-[(4-Chlorophenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinyl]amino}-4-methyl-5-thiazolecarboxylic acid ethyl ester



the use of the appropriate amine in step C1.1.

Table C

Ex.	Z	Name	HPLC Retention ^a (min)	MS Reported
C2		2-{4-(4-Hydroxy-piperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.30	537.57
C3		4-Methyl-2-{4-[(tetrahydrofuran-2-ylmethyl)-amino]-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-thiazole-5-carboxylic acid ethyl ester	1.58	537.34
C4		4-Methyl-2-{4-morpholin-4-yl-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-thiazole-5-carboxylic acid ethyl ester	1.55	523.22
C5		2-{4-(3-Carbamoyl-piperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.427	564.36
C6		2-{4-(4-Hydroxymethylpiperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.443	551.36
C7		2-{4-(2-Hydroxymethyl-1-pyrrolidinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.55	536.62
C8		2-{4-(3-N,N-Diethylcarbamoyl-1-piperidinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino}-4-methyl-thiazole-5-carboxylic acid ethyl ester	1.73	619.75

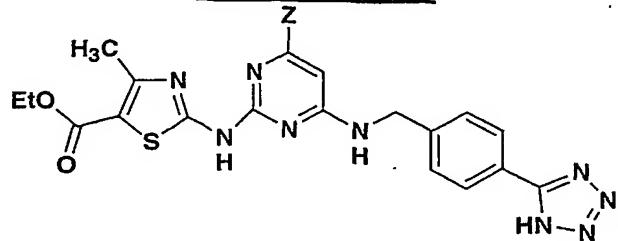
**C1.2**

A solution of compound **C1.1** (117.0 mg, 0.3 mmol) and 4-cyanobenzylamine (86.0 mg, 0.65 mmol) in *n*-butanol (2.0 ml) was heated to 130°C overnight. After cooling to room temperature, the precipitated solid was collected by filtration and purified by preparative HPLC to yield **C1.2** (118.0 mg, 81 %). HPLC: 95%, ret. time = 1.947 min., LC/MS M⁺ = 493.

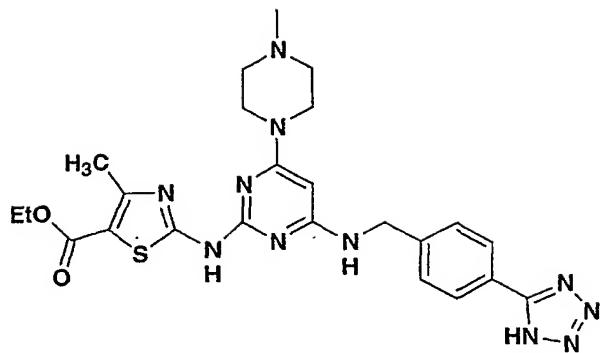
C1.3 4-Methyl-2-[4-(4-methyl-piperazin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester

Azidotrimethyltin (42.0 mg, 0.21 mmol) was added in one portion to a stirred suspension of compound **C1.2** (53.4 mg, 0.11 mmol) in *o*-xylene (0.5 mL) and heated to 115°C overnight. After cooling to room temperature the solid was filtered, washed with hot toluene and purified by preparative HPLC to yield **C1** (37.0 mg, 64%). ¹H-NMR (MeOH-*d*₄) δ: 8.24 (2H, d, J=8.5 Hz), 7.82 (2H, d, J=8.0 Hz), 5.11 (3H, br. s), 4.96 (1H, br. s), 4.52 (2H, q, J=7.0 Hz), 3.57 (4H, br. s), 3.53 (4H, br. s), 3.18 (3H, s), 2.78 (3H, s), 1.56 (3H, t, J = 7.0 Hz). HPLC: 95%, ret. time = 1.847 min., LC/MS (M+H)⁺ = 536.

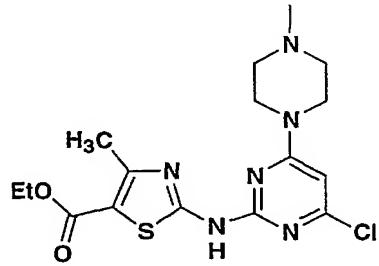
20

Example C2-C12

Examples **C2-C12** were prepared in a similar manner to that used for Example **C1**, with

**C1**

C1.1: 2-[4-Chloro-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester

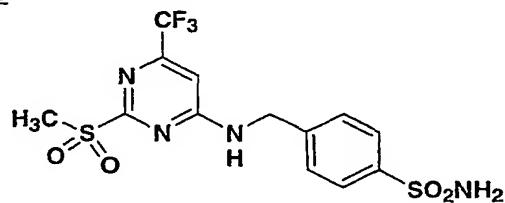
**C1.1**

A suspension of **A1.1** (600mg, 1.8 mmol), 1-methyl-piperazine (0.22 mL, 2.0 mmol) and diisopropylethylamine (1.4 mL, 7.9 mmol) in *n*-butanol (12 mL) was heated to 110°C for 10 hours. After cooling to room temperature, the precipitated solid was collected by filtration and washed with methanol to yield **C1.1** (670 mg, 94%). HPLC: 95%, ret. time = 1.403 min., LC/MS M⁺ = 397.

C1.2: 2-[4-(4-Cyano-benzylamino)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester

A mixture of **B5.1** (1.28 g, 5.60 mmol), 4-aminomethylbenzenesulfonamide hydrochloride (1.97 g, 8.85 mmol), and triethylamine (1.76 mL, 12.6 mmol) in ethanol (15 mL) was heated at 85 °C in a sealed tube for 1 h. The mixture was concentrated under vacuum. The residue was diluted with AcOEt, washed with water, 1N AcOH (twice), saturated NaHCO₃ solution (twice), and brine. The solution was then dried over anhydrous MgSO₄. Evaporation of solvent provided **B5.2** (2.10 g, 99% yield) as a white solid.

B5.3: 4-[4-(Aminosulfonyl)phenyl]methylamino]-2-methylsulfonyl-6-trifluoromethylpyrimidine



10

15

To a solution of **B5.2** (1.88 g, 4.97 mmol) in MeOH (130 mL) was added mCPBA (75 %, 3.42 g, 14.9 mmol) at rt in one portion. The resulting mixture was stirred at rt for 16 h before it was concentrated under vacuum. The residue was diluted with AcOEt, washed with 5% NaS₂O₃ solution (twice), saturated NaHCO₃ solution (twice), and brine. The solution was then dried over anhydrous MgSO₄. Evaporation of solvent provided **B5.3** (2.00 g, 98% yield) as a white solid.

20

B5.5: 1-Acetyl-5-{4-(4-methyl-piperazin-1-yl)-6-[4-(aminosulfonyl)phenyl]methylamino}pyrimidin-2-ylamino}-2,3-dihydro-1H-tetrahydroindole

25

A mixture of **B5.3** (20 mg, 0.048 mmol) and commercially available 1-Acetyl-5-amino-2,3-dihydro-(1H)indole (84 mg, 0.48 mmol) was fused at 175 °C for 20 min. After cooling to rt, the mixture was dissolved in a minimum amount of DMSO, diluted with MeOH, and applied to preparative HPLC. **B5** (16 mg, 46% yield) was obtained as a lyophilized powder as a 2 eq. TFA salt. (M + H)⁺ = 507.09.

30

Example C1

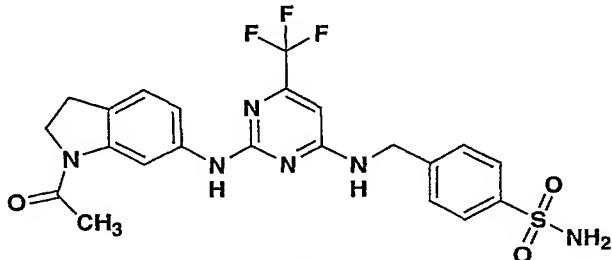
4-Methyl-2-{4-(4-methyl-piperazin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]pyrimidin-2-ylamino}-thiazole-5-carboxylic acid ethyl ester

^aHPLC conditions used to determine retention times; 4 min gradient 0-100% B in A(A; 0.1% TFA in 90/10 water/methanol; B; 0.1%TFA in 10/90 water/methanol) using a YMC turbopack column at 254 nm. * Waters Xterra 4.6x30 5u C18 (2min) Solvent A and B as above.

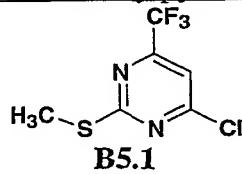
5

Example B5

1-Acetyl-5-[4-(4-methyl-piperazin-1-yl)-6-[[(4-aminosulfonyl)phenyl]methyl]amino]pyrimidin-2-ylamino]-2,3-dihydro-1H-tetrahydroindole



10

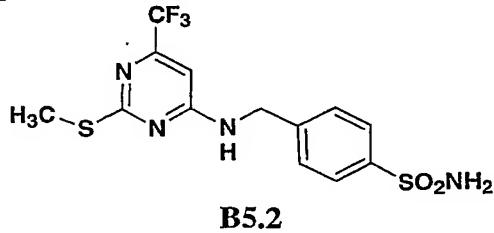
B5B5.1: 4-Chloro-2-methylthio-6-trifluoromethylpyrimidine

15

B5.1

A mixture of commercially available 4-hydroxy-2-methylthio-6-trifluoromethylpyrimidine (2.00 g, 9.52 mmol) and POCl₃ (10 mL) was heated at reflux for 1.5 h. The excess POCl₃ was removed under vacuum. The residue was dissolved in AcOEt, washed with cold water, saturated NaHCO₃ solution, cold water, and brine. The solution was then dried over anhydrous MgSO₄. Evaporation of solvent provided **B5.1** (1.31 g, 60% yield) as a colorless oil.

25

B5.2: 4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-2-methylthio-6-trifluoromethylpyrimidine**B5.2**

A solution of **B1.2** (70 mg, 0.19 mmol) and 4-methylsulfonylbenzylamine hydrochloric salt (66 mg, 0.285 mmol), diisopropylethylamine (111mg, 0.855 mmol) in N-methyl-2-pyrrolidine (2 mL) was heated to 120 to 130°C for two hours. The reaction mixture was concentrated to yield a crude product which was purified with prep. 5 HPLC (reverse phase) to yield **B1** (38 mg, 32 %). $^1\text{H-NMR}$ (CD_3OD) δ : 7.78 (2H, d, $J = 8$ Hz), 7.52 (2H, d, $J = 8$ Hz), 4.92 (2H, s), 4.17 (2H, q, $JJ=7$ Hz), 4.03 (2H, m), 3.45 (2H, m), 2.93-2.98 (8H, m), 2.40 (3H, s), 1.18 (3H, t, $J = 7$ Hz). HPLC: 98%, ret. time = 1.58 min., LC/MS (M+H) $^+$ = 517.

Example B2-B4

10

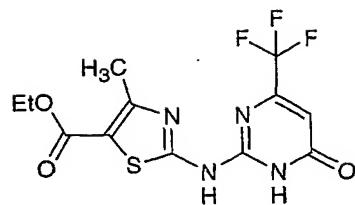


Examples **B2-B3** were prepared in a similar manner to that used for Example **B1**, with the use of the appropriate *beta*-ketoester in step **B1.1**, and the appropriate amine in step **B1.3**.

15

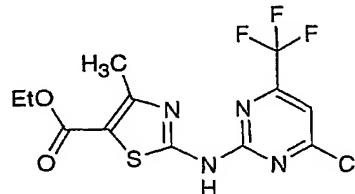
Table B

Ex.	L	Z	Name	HPLC Retention ^a (min)	MS Reported
B2		(CH ₃) ₂ CH-	2-[4-Isopropyl-6-(4-sulfamoylbenzylamino)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester	2.55	491.18
B3		CH ₃ -	4-Methyl-2-[4-(4-sulfamoylbenzylamino)-6-methylpyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester	2.23	463.18
B4		HOCH ₂ -	4-Methyl-2-[4-(4-sulfamoylbenzylamino)-6-hydroxymethyl-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester	1.35	479

**B1.1**

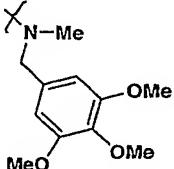
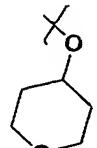
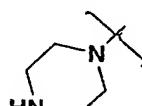
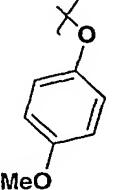
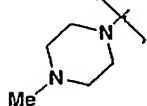
A solution of **A1.1** (125 mg, 0.731 mmol), ethyl trifluoroacetoacetate (167 mg, 5 0.731 mmol) and sodium ethoxide(21% in ethanol, 0.989 ml, 2.65 mmol) in DMA was heated to 100°C for 1 hr and then it was cooled down to RT. The reaction mixture was diluted with 2 mL of water, and neutralized with 1 N HCl. The solid was collected by filtration and dried to yield **B1.1** (150 mg, 59%).

10 **B1.2: 2-(4-Chloro-6-trifluoromethyl-pyrimidin-2-ylamino)-4-methyl-thiazole-5-**
carboxylic acid ethyl ester

**B1.2**

15 A solution of **B1.1** (150 mg, 0.429 mmol) in POCl_3 (1 ml) was heated to 100°C for 2 hours and then it was cooled down to RT which was poured into 10 ml of ice-water. It was neutralized with NaOH to pH about 9. The solid was collected with filtration and then it was added to 10 ml of methanol and stirred about 10 minutes. The solid was filtered off. The mother solution was concentrated to yield the desired product **B1.2** (70 20 mg, 44.3%). LC/MS ($\text{M}+\text{H}$)⁺ = 368.

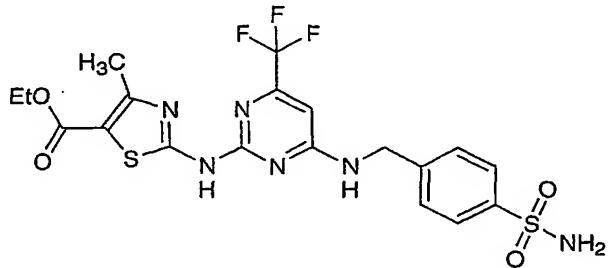
25 **B1.3: 4-Methyl-2-[4-(4-methyl-piperazin-1-yl)-6-[[4-(aminosulfonyl)phenyl]methyl]aminol]pyrimidin-2-ylamino}-thiazole-5-carboxylic acid ethyl ester**

A212			2-[[4-[4-tetrahydropyranyl]oxy-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.95 ^c	574.26
A213		-NH ₂	2-[[4-[1-piperazinyl]-6-amino-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.07	364.14
A214			2-[[4-[4-Methyl-1-piperazinyl]-6-[(4-methoxyphenyl)oxy]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.63 ^c	485.23

^aHPLC conditions used to determine retention times; 4 min gradient 0-100% B in A(A; 0.1% TFA in 90/10 water/methanol; B; 0.1%TFA in 10/90 water/methanol) using a YMC turbopack column at 254 nm. Waters Xterra 4.6 x 30 5μ C18 4 min gradient 0-100% B in A(A; 0.2% H₃PO₄ in 90/10 water/methanol; B; 0.2% H₃PO₄ in 10/90 water/methanol)^a.
 5 YMC ODS-A 4.6 X 33 (2min)^b. Phenomenex 4.6 x 30 5μ (2min)^c. Phenomenex Primesphere S5 C18 4.6 x 50 (4 min)^d.

Example B1

10 4-Methyl-2-{4-(4-methyl-piperazin-1-yl)-6-[[4-(aminosulfonyl)phenyl]methyl]amino[pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester}



15

B1

B1.1: 4-Methyl-2-(6-oxo-4-trifluoromethyl-1,6-dihydro-pyrimidin-2-ylamino)-thiazole-5-carboxylic acid ethyl ester

			5-thiazolecarboxylic acid, ethyl ester		
A206			4-Methyl-2-[4-[methyl(phenylmethyl)amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester	2.37	482.45
A207		$\text{Me}_2\text{N}-$	2-[4-(Dimethylamino)-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.31 ^b	491.45
A208			2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(3-(5-(1H)tetrazolyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.43	536.62
A209			2-[[4-[4-hydroxymethyl-1-piperidinyl]-6-[(4-(propylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.61	603.77
A210			2-[[4-[4-hydroxymethyl-1-piperidinyl]-6-[(4-(cyclopropylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.56	601.75
A211			2-[[4-[3-(Hydroxymethyl)-1-piperidinyl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester	1.48 ^b	573.47